NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

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NDA 21070

COMPANY SUBMISSION

PSYCHOMOTOR STUDIES

3.9 Psychomotor Studies

3.9.1 Overview

In clinical studies, the most common adverse experience with cyclobenzaprine 10 mg was drowsiness. Drowsiness may not be accompanied by psychomotor impairment [10]. Subjects can overcome drug-induced sedation in order to perform routine tasks. Therefore, the effects of cyclobenzaprine 5 mg on sedation and psychomotor performance were separately assessed in 6 clinical pharmacology studies. Table 35 summarizes the study designs, including the age range for the subjects who were randomized. All of the studies were double-blind, randomized, placebo-controlled, crossover trials that enrolled generally healthy subjects. A standard Visual Analog Scale (VAS) was used to subjectively measure sedation (drowsiness) in each study. One study (Protocol 012) also included the Multiple Sleep Latency Test (MSLT), a measure of a subject's ability to fall asleep in an unstimulated environment. Computerized batteries of standardized psychomotor performance tests were used to directly measure psychomotor impairment (see Table 36). For the analysis, various parameters were derived from the different tests. Descriptions of the tests are provided in Appendix 1. Two of the studies (Protocols 001 and 003) were published and reprints are provided as Attachments to this document.

3.9.1 Overview (Cont.)

Table 35

Overview of Psychomotor Studies

Protocol Number	N	Age Range (years)	Tests Performed	Treatments	CYC Dosing
001 [28]	24	18 to 29	VAS Psychomotor	CYC 5 CYC 2.5 DPH 50 Placebo	One dose
002	18	21 to 43	VAS Psychomotor	CYC 5 Placebo	t.i.d. for 10 doses
003 [27]	17	62 to 80	VAS Psychomotor	CYC 5 DPH 50 Placebo	t.i.d. for 10 doses
012	28	18 to 50	VAS MSLT Psychomotor	CYC 5 DPH 50 CLM 1 Placebo	t.i.d. for 4 doses
014	32	65 to 82	VAS Driving-related psychomotor tests	CYC 5 DPH 50 AMI 50 Placebo	t.i.d. for 4 doses
015	32	21 to 39	VAS Driving-related psychomotor tests	CYC 5 DPH 50 AMI 50 Placebo	t.i.d. for 4 doses

CYC = Cyclobenzaprine.
DPH = Diphenhydramine.
AMI = Amitriptyline.
CLM = Clemastine.

VAS = Visual Analog Scales.
MSLT = Multiple Sleep Latency Test.

3.9.1 Overview (Cont.)

Table 36

Summary of Performance Tests in Psychomotor Studies

Test	Parameter	Protocol Number					
		001	002	003	012	014	015
Auditory sustained attention	Auditory sustained attention	X	X	X			
Visual sustained attention	Visual Sustained Attention (False Alarms)	X	X	X			
	Visual Sustained Attention (hits)	X	X	X			
Choice reaction time	Mean recognition time	X	X	X	X		
	Mean reaction time	X	X	X	X		
	Total reaction time	X	X	X	X		
Continuous performance	Continuous performance	X	X	X			
Finger tapping	Finger tapping	X	X				
Verbal free recall	Verbal free recall	X	X	X			
Delayed recall and recognition	Delayed recall	X	X	X			
	Delayed recognition	X	X				
Digit span	Digit span forwards	X	X				
	Digit span backwards	X	X				
Critical flicker fusion threshold	Critical flicker fusion	X	X				
Digit symbol substitution	Digit symbol substitution			X	X		
Critical tracking task	Lambda score					X	X
Vigilance task	Response time					X	X
	Number of errors					X	X
Divided attention task	Performance score					X	X
	Response time					X	X
	Mean absolute tracking error					X	X
	Number of errors					X	X

3.9.1 Overview (Cont.)

Exploratory Studies: The first study, Protocol 001, compared single doses of cyclobenzaprine 5 mg and 2.5 mg with diphenhydramine 50 mg, a nonprescription antihistamine known to have sedating properties. Subjects completed a standard series of 16 visual analog scales (including an Alert-Drowsy scale) to provide a full assessment of the medications' effects on mood [13]. A screening battery of 9 psychomotor tests was completed once in each treatment period. All tests were performed between 2 and 3 hours postdose to correspond with peak plasma concentrations of diphenhydramine and cyclobenzaprine. The results showed that cyclobenzaprine 5 mg was associated with less sedation and psychomotor impairment than diphenhydramine 50 mg within the 3-hour postdose period in healthy, young subjects.

Protocol 002, the second study, examined whether accumulation of cyclobenzaprine with repeated dosing is accompanied by increasing sedation [28]. Subjects received cyclobenzaprine 5 mg t.i.d. (10 doses) or placebo. The visual analog scales and psychomotor tests used in Protocol 001 were administered in this study. Cyclobenzaprine 5 mg t.i.d. for 4 days was not associated with clinically significant changes in measures of sedation or psychomotor performance.

Increasing age may be associated with an increased susceptibility to the sedating effects of medications. Protocol 003 was conducted in order to examine the sedative and psychomotor effects of multiple doses of cyclobenzaprine in healthy elderly volunteers [27]. Subjects received cyclobenzaprine 5 mg t.i.d. for 10 doses, diphenhydramine 50 mg t.i.d. for 10 doses, and placebo. The visual analog scales and psychomotor tests used in Protocols 001 and 002 were administered on multiple occasions over the 4 days of dosing in Protocol 003. Neither cyclobenzaprine 5 mg nor diphenhydramine 50 mg were associated with consistent meaningful changes in the measures of sedation or psychomotor performance. The absence of sedation with diphenhydramine in elderly subjects was consistent with an earlier published study of diphenhydramine [15].

The first 3 studies provided limited information about the time course of sedation after a single dose of cyclobenzaprine. Protocol 002 also did not compare sedation after the first dose with that on the second day of dosing. Approximately 10% of patients receiving cyclobenzaprine 5 mg in the Phase III studies reported somnolence beginning on the second day of dosing (see Table 23). It was therefore of interest to further investigate the time course of effects with single and multiple doses of cyclobenzaprine 5 mg.

Sleep Latency and Psychomotor Study: The knowledge from the first 3 psychomotor studies and the Phase III studies were incorporated in the design of Protocol 012. This study compared cyclobenzaprine 5 mg with two nonprescription antihistamines: diphenhydramine 50 mg and clemastine 1 mg. The comparison of cyclobenzaprine and clemastine was of interest since both have a long half-life. The test battery was limited to

3.9.1 Overview (Cont.)

1 visual analog scale and 2 psychomotor tests in order to permit retesting at 2-hour intervals after the first and fourth doses of cyclobenzaprine. The Multiple Sleep Latency Test (MSLT) was included to measure objectively the time it took to fall asleep. Since neither the Alert-Drowsy visual analog scale nor the MSLT assess psychomotor performance, two psychomotor tests (Choice Reaction Time and Digit Symbol Substitution) were administered at each time point. The psychomotor tests were selected based on published data showing the tests were sensitive to the effects of diphenhydramine 50 mg [20].

Protocol 012 showed that sedation with cyclobenzaprine 5 mg is generally similar after the first and fourth doses. Peak drowsiness with diphenhydramine occurred at 2 hours postdose, while peak drowsiness with cyclobenzaprine occurred at 4 to 6 hours postdose. All of the active treatments produced similar amounts of drowsiness as measured by visual analog scale. Cyclobenzaprine 5 mg, however, shortened the time it took to fall asleep in an unstimulated environment to a greater extent (1 to 2 minutes) than diphenhydramine or clemastine. There appeared to be adaptation to the sedating effect of diphenhydramine as measured by MSLT. All of the active treatments were equivalent to each other and placebo with regard to the planned analyses of the psychomotor tests (peak and overall scores over the entire period). Analysis of the data for individual time points, however, showed significant differences between diphenhydramine and placebo in reaction time at 3 and 5 hours after the first dose, and between cyclobenzaprine and placebo in reaction time 5 hours after the first dose. Cyclobenzaprine and diphenhydramine were not significantly worse than placebo in the Digit Symbol Substitution test, a measure of memory and cognition.

Protocol 012 confirmed that cyclobenzaprine and diphenhydramine have different time courses with respect to sedation. The MSLT test measured the ability to fall asleep when instructed to do so, but the study did not include a rigorous measure of vigilance, the ability to stay awake when a situation or task requires alertness or mental acuity.

Driving-Related Skills Studies: While drowsiness in itself can be bothersome, the consequence of greatest potential concern is impairment of skills related to daily activities such as driving. It is generally agreed that patients should not drive while taking medications that may produce sedation; however, some patients may disregard this advice. Therefore, two psychomotor studies were conducted to directly assess the potential of cyclobenzaprine 5 mg to impair functional skills related to driving. Protocol 015 evaluated people aged 21 to 49, and Protocol 014 enrolled subjects who were aged 65 or older. A validated battery of psychomotor tests was administered [32]. This battery has been shown to be sensitive to the effects of various blood alcohol levels. The 1.5-hour battery evaluated the ability to control movement of a machine in use (Critical Tracking), ability to simultaneously perform tracking and visual search (Divided

3.9.1 Overview (Cont.)

Attention), and ability to maintain attention to a boring task over a long period of time (Vigilance) [21]. Response time was measured as part of the Divided Attention and Vigilance tests. Amitriptyline 50 mg and diphenhydramine 50 mg were included as positive controls [31]. (Diazepam was not included as a positive control because of the potential for paradoxical reactions.) Testing began 4 hours after cyclobenzaprine 5 mg was administered in order to measure performance at the expected time of peak impairment based on the previous studies. In both Protocols 014 and 015, psychomotor performance with cyclobenzaprine 5 mg was generally similar to placebo and not worse than diphenhydramine 50 mg. Amitriptyline clearly produced more sedation and impairment than either cyclobenzaprine or diphenhydramine. These findings suggest that cyclobenzaprine 5 mg should not be associated with more impairment of driving-related skills than occurs with currently available sedating antihistamines currently available OTC. The effect of cyclobenzaprine 5 mg is similar to placebo and distinctly different from a strongly sedating drug such as amitriptyline 50 mg.

Organization of Psychomotor Study Review: The sections that follow present the results of each of the 6 psychomotor studies. The measures of sedation in all 6 studies are discussed first, and then the psychomotor tests in all 6 studies are presented. Protocol 012 is discussed first in each section as it provides the most detailed information about the time course of effect with cyclobenzaprine 5 mg. Results of the studies in elderly subjects are presented after the results of the studies in younger subjects.

3.9.2 Sedation in Young Subjects

Four studies were performed in young subjects to characterize sedation associated with cyclobenzaprine 5 mg.

3.9.2.1 Protocol 012

This double-blind, multiple-dose, randomized, 4-treatment, 4-period crossover study provides the most comprehensive evaluation of the sedation potential of cyclobenzaprine. In order to fully characterize the extent and time course of sedation, two different types of tests were administered at multiple times over a 32-hour period. A visual analog scale (VAS) was used to subjectively assess sedation, and the Multiple Sleep Latency Test (MSLT) was used to objectively measure the ability to fall asleep when told to do so in an unstimulated environment. Two nonprescription antihistamines (diphenhydramine and clemastine) were included as active controls. Twenty-eight healthy subjects (mean age 31 years) were studied. All subjects received the following 4 treatments separated by a washout period of at least 6 days: cyclobenzaprine 5 mg, clemastine 1 mg, diphenhydramine 50 mg, or placebo. Each treatment except clemastine was administered t.i.d. for 4 doses (3 doses on Day 1 and 1 dose on Day 2). Since clemastine is approved for b.i.d. dosing, in order to maintain the study blind an identical 4-dose schedule was used, but Dose 2 was placebo.

VAS Results

The VAS consisted of a 100-mm horizontal line with the words "alert" and "drowsy" at the left and right ends, respectively. Subjects recorded a VAS rating just before Dose 1 then every 2 hours through 10 hours after Dose 1 (Dose 2 was administered 8 hours after Dose 1). On Day 2 they recorded a VAS rating before the morning dose (Dose 4) then every 2 hours until 8 hours postdose. Peak drowsiness for each subject was the maximum alert/drowsy VAS score during the study period. Overall drowsiness was the average VAS value during the study period.

A summary of the peak and overall drowsiness data is shown in Table 37. The geometric mean ratios (GMR) and 90% confidence intervals are in Table 38. For peak drowsiness as measured by VAS, the 3 active treatments were equivalent to each other; none of the 3 actives were equivalent to placebo. These data confirm the primary hypothesis that clemastine and cyclobenzaprine produce a similar level of drowsiness as measured by peak VAS (i.e., the 90% confidence interval about the geometric mean ratio for clemastine/cyclobenzaprine lies between the prespecified limits of 0.67 and 1.5). Results for overall drowsiness were similar to those for peak. All 3 active treatments caused more drowsiness than placebo, and the 3 actives were equivalent.

3.9.2.1 Protocol 012 (Cont.)

Table 37

Peak and Overall Values for Alert/Drowsy Visual Analog (VAS) Scale: Protocol 012 (N=28)

Treatment	Geometric Mean	
	Peak	Overall
Cyclobenzaprine	48.8	24.8
Diphenhydramine	46.6	23.0
Clemastine	50.8	26.0
Placebo	32.8	16.9

A higher value indicates greater sedation.
Geometric means are from the final model that included terms for sequence, subject, treatment, and period.
VAS Scale: 0 to 100 mm, 100=maximum and 0=minimum drowsiness.

Table 38

Analysis of Peak and Overall Alert/Drowsy Visual Analog Scale (VAS): Protocol 012 (N=28)

Treatment Comparison	Peak Drowsiness		Overall Drowsiness	
	GMR	90% CI	GMR	90% CI
Dph vs. Cyc	0.95	(0.78, 1.16)	0.93	(0.76, 1.12)
Clm vs. Cyc	1.04	(0.85, 1.27)	1.05	(0.87, 1.27)
Pbo vs. Cyc	0.67	(0.55, 0.82)†	0.68	(0.56, 0.83)†
Clm vs. Dph	1.09	(0.89, 1.33)	1.13	(0.93, 1.38)
Pbo vs. Dph	0.70	(0.58, 0.86)†	0.73	(0.61, 0.89)†
Pbo vs. Clm	0.65	(0.53, 0.79)†	0.65	(0.53, 0.79)†

† Confidence interval is outside the equivalency interval (0.67,1.5).
A GMR >1.00 indicates the first treatment in the comparison had higher values, indicating more sedation.
Dph=Diphenhydramine, Cyc=Cyclobenzaprine, Clm=Clemastine, Pbo=Placebo.
VAS Scale: 0 to 100 mm, 100=maximum and 0=minimum drowsiness.

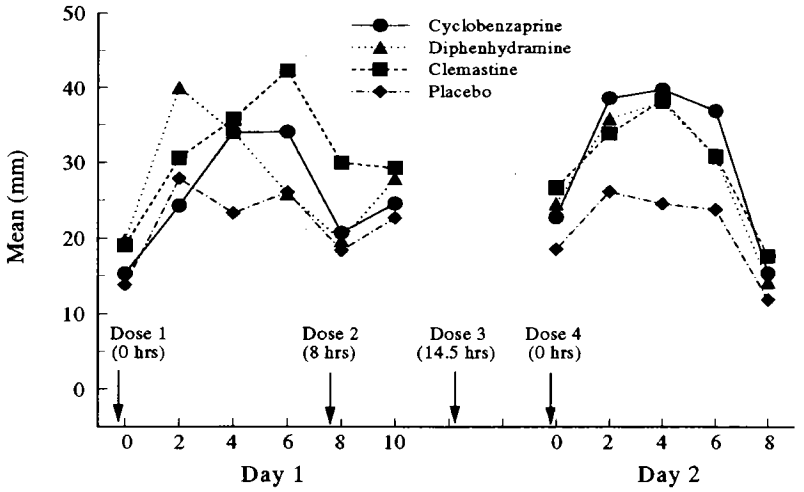
Examination of the means for the VAS by time point (Figure 5) provides information about the time course of drowsiness with each treatment. There were differences between the actives in the time course of sedation. On Day 1, peak drowsiness with diphenhydramine occurred at 2 hours after the first dose, while maximum drowsiness occurred at 4 to 6 hours with cyclobenzaprine and 6 hours with clemastine. At 2 hours, diphenhydramine was significantly more sedating than cyclobenzaprine or clemastine. On Day 2, all active treatments had their most sedating effect at 4 hours.

3.9.2.1 Protocol 012 (Cont.)

Figure 5

Mean Alert/Drowsy VAS by Time Point: Protocol 012 (N=28)

Scale: 0 = Most Alert to 100 = Most Drowsy



MSLT Results

The Multiple Sleep Latency Test (MSLT) measures the subject's propensity to fall asleep in a darkened room. Subjects were told to allow themselves to fall asleep, and polysomnographic recording techniques were used to measure the time needed to achieve sleep. When electrophysiologic criteria for sleep were achieved, the subjects were immediately awakened, and the elapsed time was recorded. If sleep was not achieved in 20 minutes, the test session was terminated and a value of 21 minutes was assigned. Test sessions were conducted at 2, 4, and 6 hours after Dose 1 and Dose 4. The standard diagnostic MSLT includes 4 test sessions in a day [12], but only 3 were conducted in this protocol in order to complete the tests before the second dose of drug was administered. Peak effect was calculated for each subject as the minimum of the 6 MSLT values measured during the study period. Overall effect was the average of the 6 values. The geometric means for peak and overall effect are given in Table 39 and the GMR and 90% confidence intervals are given in Table 40.

The usual method of reporting diagnostic MSLT results is the average of at least 4 test values over 1 day [12], but the protocol for this study prespecified that the 6 sessions from Day 1 and Day 2 would be pooled for analysis of equivalence between treatments. Considering both days, placebo had the highest mean overall values,

3.9.2.1 Protocol 012 (Cont.)

cyclobenzaprine had the lowest, and diphenhydramine and clemastine were in-between (Table 39). The confidence intervals for the GMRs were outside the prespecified equivalence range (0.67, 1.5) for comparisons of cyclobenzaprine with diphenhydramine and placebo (Table 39). The confidence interval for clemastine/cyclobenzaprine fell within the predefined range for comparability.

A similar pattern was observed for peak effect over the 2 days. The placebo group had the longest time to fall asleep, cyclobenzaprine had the shortest time, and diphenhydramine and clemastine were in-between. While the confidence intervals for the GMRs were outside the prespecified equivalence range of (0.67, 1.5) for comparisons of clemastine and cyclobenzaprine with placebo and diphenhydramine, the analysis showed that diphenhydramine was equivalent to placebo with regard to peak effect. The GMR for the cyclobenzaprine comparisons indicated that subjects fell asleep more quickly with cyclobenzaprine than clemastine or diphenhydramine.

Table 39

Multiple Sleep Latency Test: Peak and Overall Values (Minutes)—Protocol 012 (N=28)

Treatment	Geometric Means	
	Peak	Overall
Cyclobenzaprine	1.84	4.28
Diphenhydramine	2.98	5.75
Clemastine	2.39	5.37
Placebo	3.02	6.82
A lower value indicates less time to fall asleep. Note: Geometric means are from the final model that included terms for sequence, subject, treatment, and period.		

Table 40

Multiple Sleep Latency Test: Analysis of Peak and Overall Values—Protocol 012 (N=28)

Treatment Comparison	Peak		Overall	
	GMR	90% CI	GMR	90% CI
Dph vs. Cyc	1.62	(1.29, 2.03)†	1.34	(1.15, 1.57)†
Clm vs. Cyc	1.30	(1.03, 1.63)†	1.26	(1.08, 1.47)
Pbo vs. Cyc	1.64	(1.30, 2.06)†	1.59	(1.37, 1.86)†
Clm vs. Dph	0.80	(0.64, 1.01)†	0.93	(0.80, 1.09)
Pbo vs. Dph	1.01	(0.80, 1.27)	1.19	(1.02, 1.39)
Pbo vs. Clm	1.26	(1.00, 1.59)†	1.27	(1.09, 1.48)
† Confidence interval is outside the equivalency interval (0.67,1.5). A GMR <1.00 indicates that the first treatment in the comparison had lower values, indicating more sedation. Dph = Diphenhydramine, Cyc = Cyclobenzaprine, Clm = Clemastine, Pbo = Placebo.				

3.9.2.1 Protocol 012 (Cont.)

In summary, this study shows that drowsiness, as measured by self-report using a visual analog scale, is similar with cyclobenzaprine 5 mg, clemastine 1 mg, and diphenhydramine 50 mg. Cyclobenzaprine, however, reduces the time it takes to fall asleep to a greater extent than diphenhydramine or clemastine on the second day of dosing.

3.9.2.2 Protocol 001

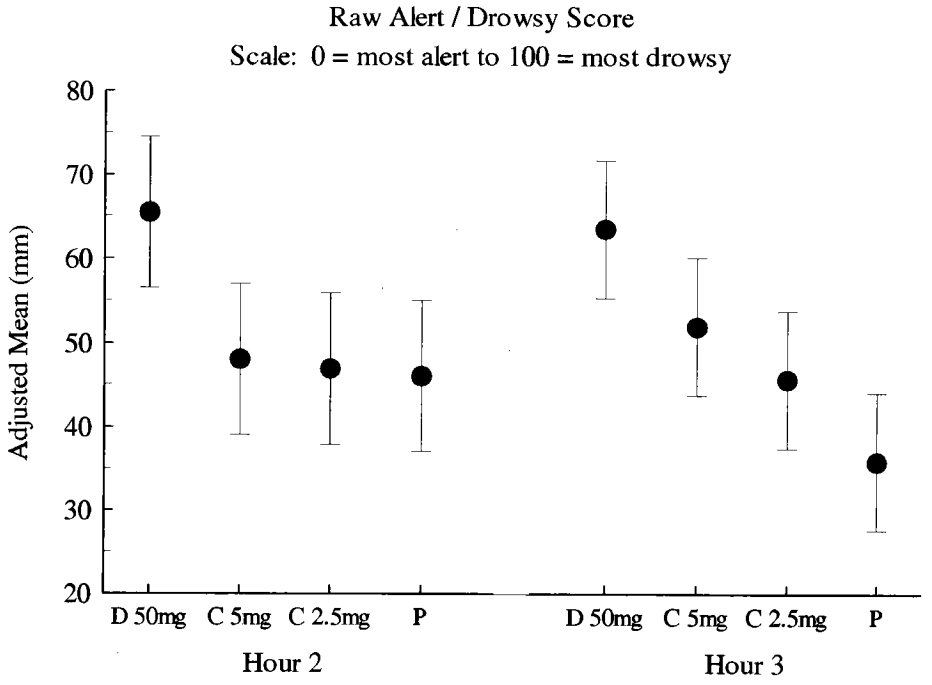
This double-blind, randomized, 4-period crossover trial studied the effects of single doses of cyclobenzaprine 5 mg, cyclobenzaprine 2.5 mg, diphenhydramine 50 mg, and placebo in 24 healthy subjects (mean age 22 years). Sedative/cognitive effects were assessed by administering a series of 16 Visual Analog Scales at 2 and 3 hours postdose (approximate times of peak plasma concentration for cyclobenzaprine and diphenhydramine). These standardized scales represented a range of subjective feelings and were used to derive 3 Factors (Alertness, Contentedness, and Calmness) [13]. One of the scales used to derive the Alertness Factor was a 100-mm Alert-Drowsy scale. Analysis of the Contentedness and Calmness factors generally did not show significant differences between placebo and either dose of cyclobenzaprine.

Figure 6 displays the Alert/Drowsy adjusted means and 95% Confidence Intervals by treatment group for each time point. The diphenhydramine group was associated with more sedation than placebo and both cyclobenzaprine doses at 2 and 3 hours. The cyclobenzaprine 5-mg group was first significantly different than placebo at Hour 3; cyclobenzaprine 2.5 mg was not significantly different than placebo at either time point. These results indicate that onset of sedation with diphenhydramine occurs before that with cyclobenzaprine 5 mg (or cyclobenzaprine 2.5 mg), and they are consistent with the results of Protocol 012.

3.9.2.2 Protocol 001 (Cont.)

Figure 6

Adjusted Means and 95% Confidence Intervals for Alert/Drowsy VAS—Protocol 001 (N=24)



D 50 mg = diphenhydramine 50 mg.
C 5 mg = cyclobenzaprine 5 mg.
C 2.5 mg = cyclobenzaprine 2.5 mg.
P = placebo.

3.9.2.3 Protocol 002

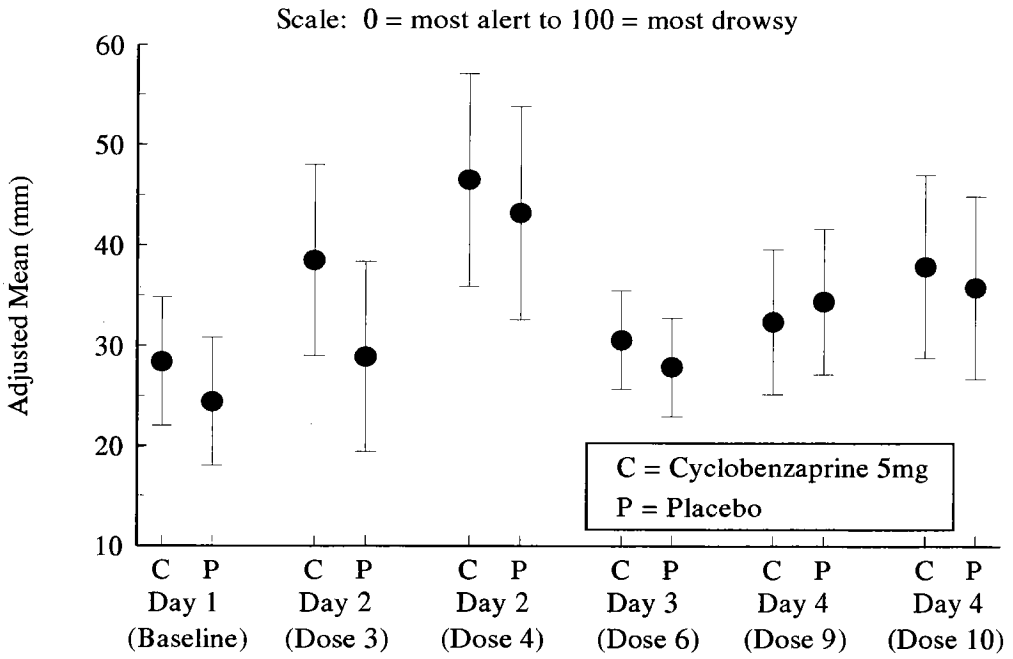
This double-blind, placebo-controlled, two-period crossover study evaluated the effects of multiple doses of cyclobenzaprine 5 mg. In view of the long half-life of cyclobenzaprine, it was questioned whether repeated dosing might result in increasing sedation over time. Eighteen healthy volunteers (mean age 27 years) were housed in the clinic for two 4-day periods with a 1-week washout between each treatment that consisted of 10 doses of cyclobenzaprine or placebo administered three times a day. They completed the battery of 16 VAS scales (identical to Protocol 001) at 6 time points: before Dose 1, before Dose 4, 2 hours after Dose 4, before Dose 7, before Dose 10, and 2 hours after Dose 10.

Figure 7 displays the Alert/Drowsy VAS adjusted means and 95% confidence intervals for each time point. The mean for cyclobenzaprine was numerically greater than for placebo at 5 of the 6 evaluations. There were no significant treatment differences with regard to the Alert/Drowsy VAS or any of three derived factors (Alertness, Contentedness, Calmness). It is unclear why this study did not demonstrate significant ($p \leq 0.050$) sedation with cyclobenzaprine at any time point. One possible explanation for the lack of sensitivity is that boredom during sequestration in the clinic had a greater impact on the level of sedation than the treatment did. The absence of a positive control in this study makes further interpretation difficult.

3.9.2.3 Protocol 002 (Cont.)

Figure 7

Adjusted Means and 95% Confidence Intervals for Alert/Drowsy VAS—Protocol 002 (N=18)



3.9.2.4 Protocol 015

Thirty-two healthy subjects (mean age 28 years) completed this double-blind, double-dummy, randomized, placebo-controlled, 4-period crossover study designed to assess potential to impair psychomotor function. They received 4 doses of study medication in each period with a 7- to 21-day washout between periods. Amitriptyline 50 mg and diphenhydramine 50 mg were administered as positive controls. Four doses of cyclobenzaprine 5 mg were administered because the clinical adverse experience data shows that most patients who report sedation recall it beginning within the first 4 doses (see Table 23).

Table 41 displays the study drug administration schedule. The primary endpoints of interest in this study were psychomotor tests conducted in-clinic on Day 2 (after Dose 4). Tolerance has been shown to develop to diphenhydramine [11], and it is unclear whether tolerance also develops acutely with amitriptyline. In order to ensure the validity of the positive controls when the test battery was performed on Day 2, the

3.9.2.4 Protocol 015 (Cont.)

diphenhydramine and amitriptyline periods consisted of active drug for the last dose only (Dose 4 on Day 2) with placebo drug for all doses on Day 1. Previous experience shows that peak sedation with cyclobenzaprine and diphenhydramine 50 mg occurs at different times. In order to characterize the maximum extent of psychomotor impairment, each active drug was administered at an appropriate pretest interval on Day 2. The cyclobenzaprine and amitriptyline treatments were administered 4 hours before the start of the test battery. The diphenhydramine and placebo treatments were administered 1 hour before the test battery so that peak impairment with diphenhydramine would occur during the 1.5-hour test battery. An Alert/Drowsy VAS was completed at home 4 hours after Dose 1 and in-clinic immediately before the test battery on Day 2.

Table 41

Study Drug Administration Schedule in Protocol 015

	Cyclobenzaprine Treatment Period	Amitriptyline Treatment Period	Diphenhydramine Treatment Period	Placebo Treatment Period
Day 1: Dose 1 (at 8 to 9 AM) Dose 2 (at 2 to 3 PM) Dose 3 (at 8 to 9 PM)	**Each dose consisted of:** 1 tab CYC **and** 1 tab APbo **and** 1 cap DPbo	**Each dose consisted of:** 1 tab CPbo **and** 1 tab APbo **and** 1 cap DPbo	**Each dose consisted of:** 1 tab CPbo **and** 1 tab APbo **and** 1 cap DPbo	**Each dose consisted of:** 1 tab CPbo **and** 1 tab APbo **and** 1 cap DPbo
Day 2: Dose 4 Hr 0 - (at 8 to 9 AM) Hr 3 - (at 11 AM to 12 noon)	**Hr 0 dose consisted of:** 1 tab CYC **and** 1 tab APbo **Hr 3 dose consisted of:** 1 cap DPbo	**Hr 0 dose consisted of:** 1 tab CPbo **and** 1 tab AMI **Hr 3 dose consisted of:** 1 cap DPbo	**Hr 0 dose consisted of:** 1 tab CPbo **and** 1 tab APbo **Hr 3 dose consisted of:** 1 cap Diphen	**Hr 0 dose consisted of:** 1 tab CPbo **and** 1 tab APbo **Hr 3 dose consisted of:** 1 cap DPbo

CYC = Cyclobenzaprine HCl 5 mg; CPbo = Placebo to match cyclobenzaprine.
AMI = Amitriptyline 50 mg; APbo = Placebo of similar size and shape to amitriptyline.
Diphen = Diphenhydramine HCl 50 mg; DPbo = Placebo of similar size and shape to diphenhydramine.
Day 1 drug doses were self-administered from Bottles 1, 2, and 3 at home.
Day 2 drug doses (Hrs 0 and 3) were staff-administered from Bottles 4, 5, and 6 to blindfolded subjects at the clinic.

Table 42 provides summary statistics for the Alert/Drowsy VAS measured on Day 1 and Day 2. The mean scores for cyclobenzaprine were similar for both days. The mean VAS for cyclobenzaprine on Day 1 was numerically greater than for the other 3 groups (which were placebo on Day 1). On Day 2, the mean score for cyclobenzaprine was significantly

3.9.2.4 Protocol 015 (Cont.)

greater than for placebo and significantly less than for amitriptyline. The VAS score for diphenhydramine was similar to placebo on Day 2. The most likely explanation for this finding is that the full sedative effect of diphenhydramine had not yet occurred at only 1 hour after dosing. Previous studies have shown that sedation is detectable 2 hours postdose, but may not be detectable 1 hour after oral administration of diphenhydramine {152}[14].

Table 42

Summary Statistics for the Alert/Drowsy VAS—Protocol 015 (N=32)
Scale: 0 = Most Alert to 100 = Most Drowsy

Treatment Group (Day 1/Day 2)	Day 1				Day 2			
	N	Mean	Std	Med	N	Mean	Std	Med
Cyclobenzaprine/cyclobenzaprine	31	40.58	25.31	36.0	32	41.47	24.34	37.0
Placebo/placebo	32	35.09	31.58	26.0	32	29.25	23.91	23.5
Placebo/diphenhydramine	32	26.41	24.46	18.0	32	31.50	25.59	23.5
Placebo/amitriptyline	32	24.25	24.29	11.5	32	64.41	25.58	71.0
Note: A higher score represents more sedation.								

In summary, the VAS data from this study show that multiple doses of cyclobenzaprine 5 mg are associated with less sedation than a single dose of amitriptyline 50 mg, and sedation 4 hours after dosing with cyclobenzaprine is not substantially greater than that seen 1 hour after a single dose of diphenhydramine 50 mg.

3.9.2.5 Summary of Sedation in Young Subjects

Single and multiple doses of cyclobenzaprine 5 mg are associated with drowsiness, as subjectively measured by visual analog scale, in young subjects. Protocol 012 shows that peak drowsiness and overall drowsiness with cyclobenzaprine 5 mg are similar to that with 2 nonprescription antihistamines, diphenhydramine 50 mg and clemastine 1 mg. Protocol 015 shows that sedation with cyclobenzaprine 5 mg is not substantially greater than with diphenhydramine; both were shown to be appreciably less sedating than amitriptyline 50 mg. The MSLT data from Protocol 012 show that cyclobenzaprine 5 mg reduces the time it takes to fall asleep during the day. The reduction in sleep latency, which is poorly correlated with the visual analog scale data, is greater with cyclobenzaprine 5 mg than with diphenhydramine 50 mg or clemastine 1 mg. Protocols 001 and 012 show that peak sedation occurs earlier with diphenhydramine 50 mg than with cyclobenzaprine 5 mg. Protocols 012 and 015 show that sedation with cyclobenzaprine 5 mg does not increase to a meaningful extent from the first to the fourth dose. Protocol 002 also suggests that sedation does not continue to increase with multiple doses of cyclobenzaprine 5 mg, although the study was less sensitive than Protocols 012 and 015.

3.9.3 Sedation in Elderly Subjects

Two multiple-dose studies were performed in elderly subjects to address whether the elderly may have an increased sensitivity to the sedating effect of cyclobenzaprine 5 mg.

3.9.3.1 Protocol 003

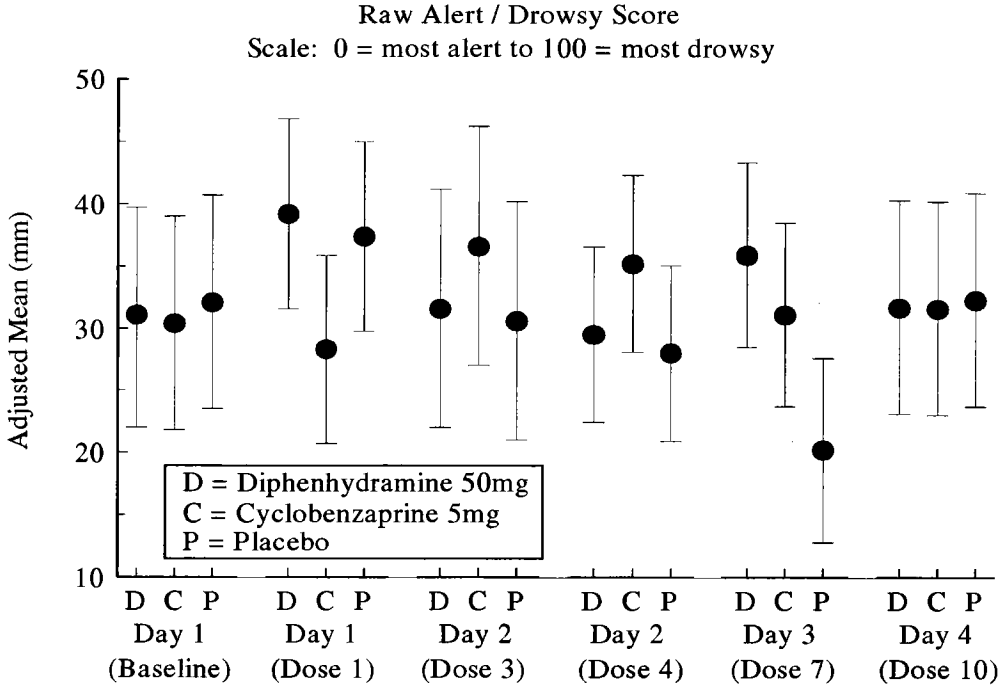
Seventeen generally healthy subjects (mean age 70 years) completed this double-blind, randomized, 3-period crossover study. Subjects received 10 doses each of cyclobenzaprine 5 mg, diphenhydramine 50 mg, and placebo; in-clinic treatment periods were separated by washout periods of at least 7 days. Subjects completed a battery of 16 VAS scales (as in Protocols 001 and 002) at 6 time points: baseline, 3 hours after Doses 1, 4, 7, and 10, and just prior to Dose 4 (6 hours after Dose 3).

There were few significant differences between treatments for the Contentedness and Calmness Factors. The results for Factor 1 (Alertness) were similar to those for the Alert/Drowsy VAS. Figure 8 displays the treatment means and 95% confidence intervals for the Alert/Drowsy VAS. Both cyclobenzaprine and diphenhydramine were significantly ($p \leq 0.050$) more sedating than placebo at only one time point (3 hours after Dose 7). These differences were not significant after a planned multiplicity adjustment (Hochberg Modified Bonferroni).

3.9.3.1 Protocol 003 (Cont.)

Figure 8

Adjusted Means and 95% Confidence Intervals for Alert/Drowsy VAS—
Protocol 003 (N=17)



In this study, neither cyclobenzaprine nor diphenhydramine was associated with significant sedation following cumulative dosing in elderly volunteers. The observation that the elderly, as a whole, may be less rather than more susceptible than the young to the sedating effect of diphenhydramine and cyclobenzaprine appears to be valid for several reasons. First, the VAS employed in this study has detected sedating effects in younger subjects in other studies. Second, a published study showed that diphenhydramine was not associated with sedation as measured by VAS in 12 elderly women [15]; this finding is definitively confirmed in Protocol 014 as discussed below.

3.9.3.2 Protocol 014

A total of 32 generally healthy subjects (mean age 70 years) completed this double-blind, double-dummy, randomized, 4-period crossover study. Both amitriptyline 50 mg and diphenhydramine 50 mg were included as active controls. The schedule of dosing administration was the same as in Protocol 015 (see Table 41). An Alert/Drowsy VAS was completed at home on Day 1 (4 hours after dose 1) and in-clinic on Day 2 (4 hours after cyclobenzaprine or amitriptyline, 1 hour after diphenhydramine or placebo).

3.9.3.2 Protocol 014 (Cont.)

Table 43 provides summary statistics for the VAS measured on Day 1 and Day 2. The Day 2 scores for cyclobenzaprine and placebo were both greater than the Day 1 scores, suggesting that boredom during the 4 hours in the clinic may have increased the VAS scores. On Day 1, the mean for cyclobenzaprine was higher than for placebo (statistical tests were not planned for Day 1). On Day 2, amitriptyline was significantly more sedating than cyclobenzaprine, diphenhydramine, or placebo. The VAS means for cyclobenzaprine (4 hours postdose) and diphenhydramine (1-hour postdose) were similar to that of placebo. These findings are validated by the finding of sedation with amitriptyline, the true positive control.

Table 43

Summary Statistics for the Alert/Drowsy VAS—Protocol 014 (N=32)

	Day 1				Day 2			
Treatment (Day 1/Day 2)	N	Mean	Std	Med	N	Mean	Std	Med
Cyclobenzaprine/cyclobenzaprine	30	36.20	29.38	31.5	32	41.66	28.01	47.0
Placebo/placebo	32	29.34	25.78	23.5	32	38.44	28.92	42.5
Placebo/diphenhydramine	32	26.06	25.92	16.5	32	37.38	30.20	32.5
Placebo/amitriptyline	32	24.53	23.44	14.5	32	66.50	26.04	76.5
Note: A higher score represents more sedation.								

3.9.3.3 Summary of Sedation in Elderly

Protocol 014 shows that the first dose of cyclobenzaprine 5 mg may be associated with mild sedation in the elderly, but this sedation is not apparent after the fourth dose. Protocol 003 showed that single and multiple doses of cyclobenzaprine 5 mg were not associated with sedation, as measured by VAS, in generally healthy elderly subjects. The VAS was administered 4 hours after taking the first dose of cyclobenzaprine in Protocol 014, and 3 hours after the first dose in Protocol 003. The slight inconsistency between the two studies with regard to whether sedation occurs after the first dose could be due to the difference in the timing of the measurements. Notwithstanding these observations in small clinical trials, it is certainly possible that some elderly individuals may be sensitive to the effects of these compounds, and in fact sedation was reported as an adverse experience by some elderly patients who received cyclobenzaprine 5 mg in the Phase III studies.

3.9.4 Psychomotor Performance in Young Subjects

Four protocols examined the extent of psychomotor impairment associated with cyclobenzaprine 5 mg in young subjects.

3.9.4.1 Protocol 012

This 4-period crossover study administered 3 psychomotor tests to subjects who remained in the clinic for 32 hours in each treatment period. As described in Section 3.9.2.1, subjects received 4 doses of cyclobenzaprine 5 mg, 4 doses of diphenhydramine 50 mg, 4 doses of placebo, and 3 doses of clemastine 1 mg. The test battery was administered at hours 1, 3, 5, 7 and 9 after the first dose, and hours 1, 3, 5, and 7 after the last dose in each period. Both the recognition time and reaction time were derived from the same test (Choice Reaction Time Test). The recognition time is the time taken for the finger to move off the central start button after the stimulus light appears, and the reaction time is the time elapsed between when the stimulus light appeared and the appropriate button was pressed. The planned analyses for all three parameters (recognition time, reaction time, and digit symbol substitution) were based on calculations of peak and overall (average) effect for each subject over the entire 32 hours. The means and geometric means for peak and overall effect with each test and treatment are shown in Table 44. All of the active treatments were equivalent to each other and placebo.

Table 44

Psychomotor Tests: Peak and Overall Values—Protocol 012 (N=28)

Measurement (Unit)	Treatment	Means (SD)		Geometric Means	
		Peak	Overall	Peak	Overall
Mean recognition time† (minutes)	Cyclobenzaprine	0.46 (0.08)	0.40 (0.06)	0.46	0.40
	Diphenhydramine	0.49 (0.18)	0.41 (0.07)	0.47	0.40
	Clemastine	0.47 (0.10)	0.41 (0.06)	0.46	0.40
	Placebo	0.44 (0.07)	0.39 (0.05)	0.44	0.39
Mean reaction time† (minutes)	Cyclobenzaprine	0.77 (0.13)	0.69 (0.09)	0.76	0.68
	Diphenhydramine	0.80 (0.25)	0.69 (0.12)	0.77	0.69
	Clemastine	0.76 (0.14)	0.69 (0.10)	0.75	0.68
	Placebo	0.74 (0.12)	0.67 (0.08)	0.73	0.66
Digit symbol substitution‡ (no. of correct squares)	Cyclobenzaprine	66.6 (9.7)	73.3 (9.6)	66.0	72.7
	Diphenhydramine	66.2 (10.0)	74.5 (8.7)	65.5	74.0
	Clemastine	67.7 (10.9)	74.8 (10.2)	66.9	74.2
	Placebo	65.9 (10.5)	73.6 (9.4)	65.1	73.0

† A higher value indicates greater psychomotor impairment.
‡ A lower value indicates greater psychomotor impairment.
Note: Geometric means are from the final model that included terms for sequence, subject, treatment, and period.

3.9.4.1 Protocol 012 (Cont.)

In an attempt to understand why the primary analyses did not show any effect for the active controls, the mean values for each of the tests were analyzed by time point. This analysis was not specified in the protocol, and no adjustments were made for multiplicity. Analysis of the individual time points provides evidence of slowed reaction time with diphenhydramine at 3 and 5 hours after the first dose but not after the fourth dose. The absence of an effect after the fourth dose may reflect adaptation or learning, which is suggested by the positive test for period effects. Cyclobenzaprine produced impairment relative to placebo only at 5 hours after the first dose, as measured by mean recognition time and mean reaction time. There were no significant differences between cyclobenzaprine and diphenhydramine in recognition time or reaction time. Clemastine also produced impairment relative to placebo at 5 hours after the first dose as measured by mean recognition time. The Digit Symbol Substitution Test measures memory and fine-motor coordination. The only impairment detected by this test was with clemastine at 3 hours after the first dose and 7 hours after the last dose, indicating that the medications generally do not affect memory and fine-motor coordination.

3.9.4.2 Protocol 015

In this placebo-controlled, 4-period crossover study, subjects received 4 doses of cyclobenzaprine 5 mg and single doses of amitriptyline 50 mg and diphenhydramine 50 mg (see Table 44). A battery of 3 tests (Divided Attention, Critical Tracking, and Vigilance) was administered once in each period at the postulated time of peak impairment for each medication (4 hours after the 4th dose of cyclobenzaprine, 4 hours after amitriptyline, 1 hour after diphenhydramine, and 1 hour after placebo). Descriptions of the tests are provided in Appendix 1.

Table 45 presents the geometric means and 95% confidence intervals for the active treatments and for placebo. The geometric means indicate that amitriptyline had the greatest amount of impairment or sedation for all 7 parameters. For the Critical Tracking lambda score, the highest geometric mean, indicating the least amount of impairment, was 4.09 for placebo. This was followed closely by the geometric mean of 4.01 for cyclobenzaprine. This ordering by impairment (placebo followed by cyclobenzaprine) was also seen with the response time and number of errors for the Vigilance Task, and the overall performance score and mean absolute tracking error for the Divided Attention Task. Comparisons of the active treatments versus placebo were secondary. Cyclobenzaprine was associated with a significantly greater degree of impairment than placebo for only one of the psychomotor parameters (tracking error on the Divided Attention Task, $p=0.020$). Amitriptyline was associated with a significantly greater degree of impairment than placebo for all 7 parameters ($p \leq 0.001$). Diphenhydramine was associated with a greater degree of impairment than placebo for 4 out of the 7 psychomotor parameters ($p \leq 0.002$).

3.9.4.2 Protocol 015 (Cont.)

Table 45

Psychomotor Tests: Geometric Means, 95% Confidence Intervals, and Comparisons Versus Placebo—Protocol 015 (N=32)

Parameter	Cyclobenzaprine Geometric Mean (95% CI)	Amitriptyline Geometric Mean (95% CI)	Diphenhydramine Geometric Mean (95% CI)	Placebo Geometric Mean (95% CI)
Critical Tracking Task				
Lambda score	4.01 (3.81, 4.21)	3.12 (2.97, 3.28)*	3.64 (3.46, 3.83)*	4.09 (3.89, 4.29)
Vigilance Task				
Response time (seconds)	1.82 (1.65, 2.02)	3.18 (2.87, 3.52)*	2.39 (2.15, 2.65)*	1.72 (1.56, 1.91)
Number of errors	8.58 (7.04, 10.45)	20.6 (16.9, 25.1)*	12.93 (10.56,15.82)*	7.00 (5.75, 8.54)
Divided Attention Task				
Overall performance score	47.9 (47.0, 48.8)	54.3 (53.3, 55.4)*	48.2 (47.3, 49.1)	47.1 (46.2, 48.0)
Response time (seconds)	3.17 (3.04, 3.30)	3.69 (3.54, 3.84)*	3.06 (2.94, 3.19)	3.15 (3.03, 3.28)
Mean absolute tracking error	2.74 (2.65, 2.83)*	3.37 (3.27, 3.48)*	2.80 (2.71, 2.90)*	2.59 (2.51, 2.68)
Number of errors	1.36 (1.15, 1.61)	2.27 (1.92, 2.69)*	1.47 (1.24, 1.74)	1.49 (1.26, 1.77)

Note: A higher lambda score represents less impairment. For all other parameters a higher score represents more impairment.
* $p \leq 0.050$ versus placebo.

3.9.4.2 Protocol 015 (Cont.)

The primary hypothesis was that multiple doses of cyclobenzaprine would be associated with peak psychomotor impairment that was no greater (i.e., within 110%) than that seen with a single dose of diphenhydramine. Impairment was measured by three primary parameters: the lambda score for the Critical Tracking Task, the response time for the Vigilance Task, and the overall performance score for the Divided Attention Task. The primary hypothesis was evaluated by an overall confidence level associated with all three parameters jointly having a true geometric mean ratio ≤1.10. The confidence level that the geometric mean ratio is ≤1.10 for each parameter individually is >0.999. The overall confidence level associated with all three parameters jointly having a true geometric mean ratio ≤1.10 is 0.999. Thus, there is a very high level of assurance that peak psychomotor impairment with cyclobenzaprine is not greater than that with diphenhydramine.

In summary, multiple doses of cyclobenzaprine 5 mg are associated with impairment of psychomotor skills related to driving that is generally similar to placebo and no greater than that seen with a single dose of diphenhydramine 50 mg.

3.9.4.3 Protocol 001

In this 4-period crossover study, subjects completed a 1-hour battery of psychomotor tests that were started 2 hours after administration of a single dose of study medication (cyclobenzaprine 5 mg, cyclobenzaprine 2.5 mg, diphenhydramine 50 mg, placebo). Analysis of variance results did indicate a possible effect due to period that was significant for eight of the 13 psychomotor test parameters. It is likely that this period effect was due to "learning" of the tests.

Diphenhydramine had the greatest negative effect on psychomotor ability and placebo had the least. In general, the effects of cyclobenzaprine 2.5 mg and 5 mg were similar and in between those of diphenhydramine and placebo. Prior to adjusting for multiplicity, the 2 doses of cyclobenzaprine did not differ significantly from each other or from placebo for any parameters except Critical Flicker Fusion and Digit Span Backwards (cyclobenzaprine 2.5 mg versus placebo). These findings are unlikely to be true clinical effects as they were not seen with the higher dose of cyclobenzaprine. Diphenhydramine differed significantly from placebo in 11 of 13 parameters, from cyclobenzaprine 5 mg in 7 parameters, and from cyclobenzaprine 2.5 mg in 8 parameters.

In summary, within the first 3 hours postdose, the level of psychomotor impairment with cyclobenzaprine 2.5 and 5 mg is similar to that of placebo and less than that with diphenhydramine 50 mg.

3.9.4.4 Protocol 002

In this 2-period crossover study, subjects received 10 doses of cyclobenzaprine 5 mg and placebo while housed in-clinic. They completed the same battery of psychomotor tests twice during each 4-day period: 2 hours after Dose 4 and 2 hours after Dose 10. There was a significant period effect for 8 of the 24 psychomotor parameters and time points. A summary of the mean score and standard error for each treatment (adjusted for period and sequence effects) is presented. There were small numerical differences between cyclobenzaprine and placebo, but there was no consistent pattern. Comparing the treatments prior to adjusting for multiplicity revealed only two significant differences: cyclobenzaprine was significantly worse than placebo for Finger Tapping and Critical Flicker Fusion on Day 2 (after Dose 4). After the multiplicity adjustment, only the difference in Critical Flicker Fusion was statistically significant. The paucity of significant differences indicates that cyclobenzaprine 5 mg administered t.i.d. for 4 days is not associated with meaningful psychomotor impairment.

3.9.4.5 Summary of Psychomotor Performance in Young Subjects

There was no consistent pattern of psychomotor impairment with cyclobenzaprine 5 mg within or across the 4 studies in young subjects. In Protocol 012, the only statistically significant differences between cyclobenzaprine and placebo were in Recognition Time and Reaction Time 5 hours after the first dose, and those differences were too small to be clinically meaningful (<10% difference). In Protocol 015, the only significant difference between cyclobenzaprine 5 mg and placebo was in mean absolute tracking error, a secondary parameter, 4 hours after the fourth dose. There were no significant differences between cyclobenzaprine 5 mg and placebo in reaction time measures in Protocols 001 and 002. After adjusting for multiplicity, cyclobenzaprine 5 mg was significantly different than placebo in Critical Flicker Fusion and Finger Tapping at 1 time point (after the fourth dose) in Protocol 002. Cyclobenzaprine 2.5 mg (but not 5 mg) was significantly different than placebo in Critical Flicker Fusion in Protocol 001 before, but not after, adjusting for multiplicity. Critical Flicker Fusion is a visual processing test that measures ability to detect discrete sensory data (a flickering light), while Finger Tapping is a psychomotor test that has little to do with cognitive function [21]. Intuitively, neither of those tests appears to measure skills directly relevant to driving. Protocol 015 showed that cyclobenzaprine 5 mg did not affect driving-related skills such as maintaining vigilance and performing simultaneous tasks (Divided Attention), skills that were significantly impaired by amitriptyline, the positive control. Taken together, the 4 studies show that cyclobenzaprine 5 mg generally does not produce meaningful psychomotor impairment in young subjects. Psychomotor performance with cyclobenzaprine 5 mg was better than with amitriptyline 50 mg, and not worse than with diphenhydramine 50 mg.

3.9.5 Psychomotor Performance in Elderly Subjects

Two studies examined psychomotor performance in elderly subjects who received cyclobenzaprine 5 mg.

3.9.5.1 Protocol 014

In this placebo-controlled, 4-period crossover study, elderly subjects (≥65 years old) received four doses of cyclobenzaprine 5 mg and single doses of amitriptyline 50 mg and diphenhydramine 50 (see Table 41). A battery of 3 tests (Divided Attention, Critical Tracking and Vigilance) was administered once in each period at the postulated time of peak impairment for each medication (4 hours after the fourth dose of Cyclobenzaprine, 4 hours after the amitriptyline, 1 hour after the diphenhydramine, and 1 hour after placebo). Table 46 presents the geometric means and 95% confidence intervals for the active treatments and for placebo. The geometric means indicate that amitriptyline had the greatest amount of impairment for all 7 parameters. For the response time and number of errors for the Vigilance Task, the placebo group had the least amount of impairment followed by the cyclobenzaprine group. The geometric means for the overall performance score, response time, and tracking error for the Divided Attention Task were nearly identical for the cyclobenzaprine and placebo groups. Cyclobenzaprine was associated with a significantly greater degree of impairment than placebo for the Critical Tracking Task lambda score ($p=0.005$) and the number of errors for the Vigilance Task ($p=0.039$). Amitriptyline was associated with a significantly greater degree of impairment or sedation than placebo for all parameters ($p<0.001$), except the number of errors for the Divided Attention Task ($p=0.062$). Diphenhydramine was associated with a significantly greater degree of impairment than placebo for the response time and number of errors for the Vigilance Task ($p<0.001$).

3.9.5.1 Protocol 014 (Cont.)

Table 46

Psychomotor Tests: Geometric Means, 95% Confidence Intervals, and Comparisons Versus Placebo- Protocol 014 (N=32)

Parameter	Cyclobenzaprine Geometric Mean (95% CI)	Amitriptyline Geometric Mean (95% CI)	Diphenhydramine Geometric Mean (95% CI)	Placebo Geometric Mean (95% CI)
Critical Tracking Task				
Lambda score	2.97 (2.87, 3.08)*	2.54 (2.45, 2.63)*	3.06 (2.95, 3.17)	3.20 (3.09, 3.31)
Vigilance Task				
Response time (seconds)	1.85 (1.67, 2.06)	2.98 (2.68, 3.31)*	2.35 (2.12, 2.61)*	1.65 (1.49, 1.83)
Number of errors	11.62 (9.33, 14.46)*	25.23 (20.27, 31.40)*	16.49 (13.25, 20.53)*	8.34 (6.70, 10.38)
Divided Attention Task				
Overall performance score	48.4 (47.3, 49.5)	53.5 (52.3, 54.7)*	47.9 (46.8, 49.0)	48.2 (47.1, 49.3)
Response time (seconds)	4.46 (4.30, 4.62)	4.93 (4.76, 5.11)*	4.35 (4.20, 4.51)	4.48 (4.32, 4.64)
Mean absolute tracking error	4.44 (4.31, 4.57)	4.91 (4.77, 5.06)*	4.49 (4.36, 4.63)	4.45 (4.32, 4.59)
Number of errors	4.15 (3.47, 4.96)	5.62 (4.70, 6.72)	3.45 (2.88, 4.12)	4.40 (3.68, 5.27)

Note: A higher lambda score represents less impairment. For all other parameters a higher score represents more impairment.
* $p \leq 0.050$ versus placebo.

3.9.5.1 Protocol 014 (Cont.)

The primary hypothesis was whether multiple doses of cyclobenzaprine were associated with peak psychomotor impairment that was no greater (i.e., within 110%) than that seen with a single dose of diphenhydramine. Impairment was measured by three primary parameters: the lambda score for Critical Tracking Task, the response time for the Vigilance Task, and the overall performance score for the Divided Attention Task. The primary hypothesis was evaluated by an overall confidence level associated with all three parameters jointly having a true geometric mean ratio ≤ 1.10. The confidence level that the geometric mean ratio is ≤ 1.10 for each parameter individually is ≥ 0.996. The overall confidence level associated with all three parameters jointly having a true geometric mean ratio ≤ 1.10 is 0.999. Thus, there is a very high level of assurance that peak psychomotor impairment with cyclobenzaprine is not greater than that with diphenhydramine.

In summary, multiple doses of cyclobenzaprine 5 mg are associated with impairment of psychomotor skills related to driving in elderly subjects that is no greater than that seen with a single dose of diphenhydramine 50 mg. Psychomotor impairment with multiple doses of cyclobenzaprine 5 mg and single doses of diphenhydramine 50 mg is similar to that with placebo in elderly subjects. These findings are validated by the demonstration of appreciable impairment with amitriptyline 50 mg, and they are consistent with the results of Protocol 003.

3.9.5.2 Protocol 003

Seventeen generally healthy elderly (ages 60 to 85 years) subjects completed this 3-period crossover study. Subjects received 10 doses each of cyclobenzaprine 5 mg, diphenhydramine 50 mg, and placebo. A computerized battery of psychomotor tests was administered twice during each period: 2 hours after Dose 1, and 2 hours after Dose 10. For the analysis, ten test parameters were derived from the 7 psychomotor tests. There was a significant period effect for 9 of the 20 tests, suggesting a learning effect. Comparing the treatments prior to adjusting for multiplicity revealed few significant treatment differences. For Visual Sustained Attention (False Alarms) on Day 1 (Dose 1), both diphenhydramine 50 mg and cyclobenzaprine 5 mg produced significantly more impairment than placebo. For Visual Sustained Attention (Hits) on Day 1 (Dose 1), diphenhydramine 50 mg caused a significant amount of impairment compared to cyclobenzaprine 5 mg. After the multiplicity adjustment there were no significant treatment differences. These data indicate that in normal elderly subjects, cyclobenzaprine 5 mg and diphenhydramine 50 mg t.i.d. for 4 days are not associated with meaningful psychomotor impairment.

3.9.5.3 Summary of Psychomotor Performance in Elderly Subjects

In Protocol 014, cyclobenzaprine 5 mg was associated with statistically significant differences versus placebo in Critical Tracking lambda score and the number of errors on the Vigilance Task. The difference between cyclobenzaprine and placebo in the lambda score was less than 10%, the predefined criteria for a clinically meaningful difference in that protocol. All 3 active treatments (cyclobenzaprine, diphenhydramine, and amitriptyline) had significantly more errors on the Vigilance Task than placebo, suggesting that parameter may be the most sensitive of those in the battery with regard to effects of central nervous system depressants in the elderly. In Protocol 003, both cyclobenzaprine 5 mg and diphenhydramine 50 mg were associated with significantly more errors than placebo (before adjusting for multiplicity) in the Visual Sustained Attention Test after the first dose. The Visual Sustained Attention Test is a measure of vigilance, so the results of the 2 studies are consistent with each other. Overall, however, cyclobenzaprine was associated with few significant differences versus placebo in either study. Psychomotor performance with cyclobenzaprine and diphenhydramine was generally similar, and clearly better than with amitriptyline 50 mg.

3.9.6 Conclusions From Psychomotor Studies

Based on the results of the 6 psychomotor studies, the following conclusions can be made:

1. Drowsiness, as subjectively measured by visual analog scale, with cyclobenzaprine 5 mg is similar to that with diphenhydramine 50 mg and clemastine 1 mg and less than that with amitriptyline 50 mg in young, healthy subjects.

2. Peak drowsiness after a single dose occurs earlier with diphenhydramine 50 mg (~2 hours) than with cyclobenzaprine 5 mg (~4 to 6 hours) or clemastine 1 mg (~6 hours).

3. Drowsiness does not continue to increase with multiple doses of cyclobenzaprine 5 mg.

4. Generally healthy elderly subjects do not appear to have an increased propensity to develop sedation with cyclobenzaprine 5 mg.

5. Cyclobenzaprine 5 mg shortens the time to fall asleep, as measured by the Multiple Sleep Latency Test, to a greater extent than does diphenhydramine 50 mg and clemastine 1 mg.

6. Compared to placebo, cyclobenzaprine 5 mg generally does not produce psychomotor impairment in young or elderly subjects. Psychomotor performance with cyclobenzaprine 5 mg is better than with amitriptyline 50 mg, similar to placebo, and not worse than with diphenhydramine 50 mg.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

SAFETY DISCUSSION

3.10 Safety Discussion

Cyclobenzaprine 5 mg was generally well tolerated in the nonprescription clinical studies. There were no serious drug-related clinical or laboratory adverse experiences. One patient died, and her death was attributed to diabetes, coronary artery disease, and cocaine use, not to cyclobenzaprine use. There were no drug-related adverse experiences that were not already reported to occur with the prescription dose of cyclobenzaprine 10 mg.

Clinical Studies: The most common adverse experience in the nonprescription cyclobenzaprine studies was somnolence. The incidence of somnolence with cyclobenzaprine was dose related in the placebo-controlled Phase III studies. Somnolence was reported by 38% of patients receiving cyclobenzaprine 10 mg, 29% receiving cyclobenzaprine 5 mg, 20% receiving cyclobenzaprine 2.5 mg, and 10% receiving placebo. Somnolence generally began within 2 days of initiating treatment, and most patients reported their most intense somnolence as mild or moderate. Only 2.6% of patients receiving cyclobenzaprine 5 mg reported severe somnolence. Twenty-nine patients (2.5%) who received cyclobenzaprine 5 mg discontinued treatment because of somnolence.

The second most common adverse experience with cyclobenzaprine was dry mouth. This anticholinergic effect was also dose related (incidence was 32, 21, 14, and 7% with cyclobenzaprine 10, 5, 2.5 mg, and placebo, respectively, in the placebo-controlled Phase III studies). Dry mouth prompted discontinuation of treatment in ≤1% of the patients/subjects who received cyclobenzaprine 5 mg.

Asthenia, fatigue, confusion, disorientation, dizziness, and decreased mental acuity were reported much less frequently than somnolence or dry mouth. The same pharmacologic effect may be responsible for these relatively nonspecific central nervous system disturbances as well as somnolence. The data suggests that the incidences of asthenia/fatigue and dizziness are dose related, although the relationship is less apparent than for the more common events of somnolence and dry mouth.

The open-label, Pattern-of-Use study (see Section 4.) showed that most patients will follow the proposed dosing instructions. Approximately 13% of the 449 patients used more than 3 tablets on at least 1 day, but more than 3 tablets were used on only 3% of the dosing days. The adverse experience profile for cyclobenzaprine 5 mg in this study was consistent with that in the placebo-controlled Phase III studies. Pooling the adverse experience data from the Pattern-of-Use study with that of Protocols 006 and 008 does not appreciably change the incidences of the most common adverse experiences.

3.10 Safety Discussion (Cont.)

Degree of Sedation: Based on the existing data for cyclobenzaprine 10 mg, it was anticipated that drowsiness would be the most commonly reported adverse experience with cyclobenzaprine 5 mg. In order to further characterize this effect, 6 psychomotor studies were performed. The drowsiness associated with cyclobenzaprine is believed to be mediated by antihistaminic and antimuscarinic properties. Antihistamines that are now available without prescription were included as controls to ascertain whether the degree of sedation with cyclobenzaprine 5 mg is greater than that already accepted with some nonprescription medications. The one measure common to all 6 studies was an Alert/Drowsy Visual Analog Scale (VAS). The degree of drowsiness with cyclobenzaprine 5 mg, as measured by the VAS, was similar to that with diphenhydramine 50 mg and clemastine 1 mg.

One psychomotor study included the Multiple Sleep Latency Test (MSLT). This test measures the time it takes to fall asleep in an unstimulated environment. The test indicated that single doses of cyclobenzaprine 5 mg, diphenhydramine 50 mg, and clemastine 1 mg tend to shorten the time it takes to fall asleep to a similar degree. With multiple doses, cyclobenzaprine shortens the time to fall asleep to a greater extent than does diphenhydramine 50 mg or clemastine 1 mg. It appears that tolerance develops to the sleep-inducing property of diphenhydramine, but not cyclobenzaprine, when 4 doses are administered in 24 hours. There was a poor correlation between sedation, as measured by VAS, and the time it takes to fall asleep when told to do so, as measured by MSLT.

Neither the VAS nor MSLT have been shown to predict performance impairment. A subject's ability to perform simple or complex psychomotor tasks cannot be inferred from measures of sedation. Therefore, specific batteries of performance tests were included in the 6 psychomotor studies. In 2 studies, the tasks were specifically selected to assess skills relevant to driving a motor vehicle. Cyclobenzaprine 5 mg was not associated with a consistent pattern of impairment relative to placebo in the laboratory measures of performance tested in the 6 studies. Two studies included both amitriptyline and diphenhydramine as positive controls. In those studies, amitriptyline 50 mg was worse than either cyclobenzaprine 5 mg or diphenhydramine 50 mg, which were similar to each other. These findings suggest that subjects can overcome cyclobenzaprine- or diphenhydramine-induced sedation when called upon to perform specific tasks. These data also suggest that use of cyclobenzaprine 5 mg should not be associated with psychomotor impairment that is any greater than that associated with current nonprescription medications known to produce sedation.

Postmarketing Experience: There is no pattern of deaths or arrhythmias to suggest that cyclobenzaprine has the potential for cardiac toxicity that is recognized to occur with the tricyclic antidepressants. The postmarketing surveillance data from 7607 patients identifies several nervous system and psychiatric adverse experiences that may occur

3.10 Safety Discussion (Cont.)

with cyclobenzaprine 10 mg. Hallucinations were reported by 0.2% of the patients who were asked specifically whether they had experienced them, a procedure generally recognized as likely to elicit over-reporting. One patient reported having a seizure when specifically questioned. There have been 82 patients with hallucinations and 26 patients with seizures who were reported spontaneously to the manufacturer over the 20 years of marketed use. Incidence rates cannot be calculated from the spontaneous report data, but there is no reason to believe the incidence is higher during marketed use than was observed in the formal postmarketing surveillance study.

None of the 1162 patients exposed to cyclobenzaprine 5 mg in the nonprescription studies reported hallucinations or seizures when asked about adverse experiences in an open-ended manner. There is insufficient data at the present time to clearly show that hallucinations with cyclobenzaprine are dose related. However, hallucinations are known to occur with high doses of anticholinergic drugs such as atropine and scopolamine. Dry mouth is an anticholinergic effect and is related to the dose of cyclobenzaprine. There are few reports in the WAES database of other potential antimuscarinic effects such as tachycardia (42), blurred vision (13), urinary retention (26), and an increase in intraocular pressure (1) with cyclobenzaprine 10 mg. If the anticholinergic effect of cyclobenzaprine is responsible for hallucinations seen with cyclobenzaprine, it is reasonable to postulate that they would be dose related. In that case, the incidence of hallucinations with cyclobenzaprine 5 mg should be lower than the 0.2% elicited reports with cyclobenzaprine 10 mg in the postmarketing surveillance study.

Gender, age, and race did not appear to have a meaningful impact on the adverse experience profile of cyclobenzaprine 5 mg in the nonprescription studies. One would expect elderly patients may be more susceptible to sedation and other more uncommon central nervous system effects. In fact, the incidence rates for nervous system/psychiatric adverse experiences were very similar in patients less than 65 years of age and patients 65 or older. This is consistent with the 2 psychomotor studies, which showed cyclobenzaprine 5 mg generally does not produce sedation in elderly subjects.

3.11 Safety Conclusions

1. Cyclobenzaprine 5 mg t.i.d. is generally well tolerated when used for up to 10 days to treat acute musculoskeletal spasm of the back or neck.

2. Somnolence and dry mouth are the most common adverse experiences with cyclobenzaprine. These effects are dose-related between 2.5 mg t.i.d. and 10 mg t.i.d. Most patients who report somnolence initially notice the effect on the first or second day of dosing. Most episodes of somnolence are mild or moderate in intensity; the incidence of severe somnolence is approximately 2.6% in patients treated with cyclobenzaprine 5 mg t.i.d. Somnolence resolves in some patients with continued dosing, suggesting adaptation may occur. The incidence of somnolence is not increased in elderly patients.

3.11 Safety Conclusions (Cont.)

3. Drowsiness, as subjectively measured by self-report, with cyclobenzaprine 5 mg is similar to that with diphenhydramine 50 mg and clemastine 1 mg and less than that with amitriptyline 50 mg in young, healthy subjects. Drowsiness occurs earlier with diphenhydramine 50 mg than with cyclobenzaprine 5 mg. Drowsiness does not continue to increase with multiple doses of cyclobenzaprine 5 mg.

4. Cyclobenzaprine 5 mg shortens the time to fall asleep (by 1 to 2 minutes, as measured by the Multiple Sleep Latency Test), to a greater extent than does diphenhydramine 50 mg and clemastine 1 mg.

5. Cyclobenzaprine 5 mg t.i.d. generally does not produce psychomotor impairment in young or elderly subjects. Psychomotor performance with cyclobenzaprine 5 mg is similar to placebo, better than with amitriptyline 50 mg, and not worse than with diphenhydramine 50 mg.

6. There are no clinically meaningful differences in the safety profile of cyclobenzaprine 5 mg t.i.d. with regard to age, race, or gender.

7. The safety profile of cyclobenzaprine 5 mg t.i.d. is not affected by concomitant use of nonprescription analgesics.

8. Cyclobenzaprine has very low potential for abuse and a high margin of safety in overdose.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

PATTERN OF USE DATA

4. Pattern-of-Use Data

Since the safety profile of cyclobenzaprine is related to the dose ingested, it is important to investigate how patients would actually use cyclobenzaprine if it were available without prescription. Protocol 009 was conducted in order to examine whether consumers will self-medicate with cyclobenzaprine 5 mg according to the labeling (the study was done with an earlier version of the label that included a maximum 7-day duration of treatment). This open-label, uncontrolled, 15-site study enrolled 468 patients with self-diagnosed painful muscle spasm, tightness, or soreness of the back or neck. The majority (56%) of the patients were recruited from advertisements in newspapers. Patients were interviewed by a study coordinator or physician but not examined. Patients were excluded from the trial if they:

- had previously been in a cyclobenzaprine clinical study
- had a history of heart disease, thyroid problems, or recent substance abuse, or were taking an antidepressant
- were a pregnant or nursing woman
- had a pending workman's compensation or other litigation related to their condition.

After giving informed consent, patients were given a bottle containing 30 5-mg tablets of cyclobenzaprine. They also received a diary card containing Indications, Directions, and Warnings consistent with the proposed label. The Directions read "Take one tablet every 6 to 8 hours. Do not exceed 3 tablets in 24 hours. Do not take continuously for more than 7 days." Patients recorded their medication use on the diary and provided a Global Impression of Change at the second visit (8 to 10 days after receiving study medication). This section summarizes the compliance and use data as recorded on the diaries.

Noncompliance

Patients were considered noncompliant if they did one or more of the following:

1. Took more than 3 tablets on at least 1 day.
2. Took more than 1 tablet per dose at least once.
3. Medicated t.i.d. for 8, 9, or 10 consecutive days.

4. Pattern-of-Use Data (Cont.)

Twenty-seven percent (27%) of the 449 patients who returned the diary card were considered noncompliant on at least one occasion. A summary of noncompliance by reason is presented in Table 47. Evaluation of compliance based on treatment days or doses shows that the majority of the medication was taken according to directions. Thirteen percent of patients took more than 3 tablets on at least 1 day, but more than 3 tablets in a single day were taken on only 3% of treatment days. Eleven percent of patients took more than 1 tablet per dose at least once, but less than 1% of doses consisted of more than 1 tablet.

Table 47

Pattern-of-Use Study: Summary of Noncompliance by Reason (N=449)

Noncompliance Reasons by Patient				Noncompliance Reasons by Days and Doses	
	Number (%)				Number (%)
Noncompliance for any reason†	120	(27)		Days when more than 3 tablets were taken (Total number of treatment days = 3,331)	103 (3)
Took more than 3 tablets on at least 1 day	60	(13)		Doses when more than 1 tablet was taken (Total number of doses taken = 7,473)	49 (1)
Took more than 1 tablet per dose at least once	49	(11)			
Medicated t.i.d. for 8, 9, or 10 consecutive days	38	(8)			

† Patients were deemed noncompliant if they had at least one of the three reasons given above.

Summary of Use

The distribution of number of treatment days is given in Table 48. The number of treatment days was calculated for each patient as the number of study days on which the patient took at least one tablet. These days were not necessarily consecutive. The mean number of treatment days was 7.4 with a range of 1 to 15 days. Eighty-two percent of patients used the medication for 9 days or less, and 92% used the medication for 10 days or less. Approximately half the patients (57%) used medication for 7 to 9 days. For each patient, the number of consecutive treatment days was also summarized. The number of consecutive treatment days tended to be less than the total number of treatment days. The mean number of consecutive treatment days was 6.9 with a range of 1 to 15 days. Thirty-eight patients (8%) medicated three times a day for 8, 9, or 10 consecutive days.

4. Pattern-of-Use Data (Cont.)

Table 48

Pattern-of-Use Study: Summary of Number of Treatment Days

Number of Treatment Days†	Number of Patients (N=449)		
	n	%	Cum%
1	13	3	3
2	10	2	5
3	17	4	9
4	25	6	14
5	20	4	19
6	27	6	25
7	84	19	44
8	116	26	69
9	57	13	82
10	42	9	92
11	30	7	98
12	5	1	99
13	0	0	99
14	1	<1	100
15	2	<1	100
Mean (SD)	7.4 (2.5)		
Median	8		

† Treatment days (days when patient took at least 1 tablet) are not necessarily consecutive.

The maximum number of tablets per treatment day was calculated for each patient and is summarized in Table 49. The maximum number of tablets ranged from 1 to 6, with the majority of patients (87%) taking not more than 3 tablets per day. Only 5 patients had a maximum of 5 or 6 tablets per day.

4. Pattern-of-Use Data (Cont.)

Table 49

Pattern-of-Use Study: Summary of Total Number of Tablets Per Day

Maximum Number of Tablets Per Day	Number of Patients (N=449)		
	n	%	cum %
1	39	9	9
2	89	20	29
3	261	58	87
4	55	12	99
5	3	1	100
6	2	<1	100
Mean (SD)		2.8 (0.8)	
Median		3	

The number of tablets taken during the study ranged from 1 to 30. The mean was 17 tablets. Seventy-percent of patients took 21 or fewer tablets.

Concomitant Analgesic Use

There were no restrictions imposed on study participants regarding prior or concomitant medication use. Thirty-five percent of patients (158/449) took an analgesic on one or more days after study medication was dispensed. The mean number of days an analgesic was used was 3.5 and the median was 2. The percentage of patients using an analgesic ranged from 13 to 16% over the first 7 days and then declined. Sixty-seven patients (15%) reported taking an analgesic to treat the condition they were using the study medication for (neck or back pain).

Conclusions

1. The majority of patients (>80%) will self-medicate with 3 or fewer tablets per day.

2. It appears that a 10-day period may be more consistent with the way patients will actually use the product than the 7 days recommended in the label iteration used in this study.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

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COMPANY SUBMISSION

CLINICAL PHARMACOLOGY - HUMAN PHARMACOKINETICS

5. Clinical Pharmacology—Human Pharmacokinetics and Bioavailability

This section summarizes the pharmacokinetics of cyclobenzaprine hydrochloride as well as pertinent biopharmaceutics data regarding cyclobenzaprine hydrochloride 5-mg tablets proposed for the nonprescription market.

Disposition studies conducted previously in animals and man have shown that cyclobenzaprine hydrochloride is well absorbed, is widely distributed among body tissues, and is extensively metabolized. Cyclobenzaprine is about 93% bound to human plasma proteins. Cyclobenzaprine (or metabolites) is secreted in the bile and is subject to enterohepatic circulation.

5.1 In Vitro Metabolism

Identification of the specific enzymes responsible for drug metabolism provides insight into potential drug-drug interactions, as well as pharmacokinetic variability. Likewise, it is also useful to assess the potential for a drug to inhibit oxidative metabolic pathways.

In vitro studies using human liver microsomes and a panel of selective cytochrome P-450 inhibitors and antibodies have shown that CYPs 3A4 and 1A2 are primarily responsible for cyclobenzaprine *N*-demethylation. CYP 2D6 plays only a minor role in cyclobenzaprine metabolism despite cyclobenzaprine's structural similarity to other tricyclic compounds, so the genetic polymorphism of that enzyme should not be a concern in the clinical use of cyclobenzaprine.

The potential for cyclobenzaprine to inhibit six cytochrome P-450-mediated reactions was investigated using human liver microsomes [1]. The *Ki* values were over 150 μM except for CYP 2D6 where the *Ki* value was 43 μM. The values obtained are much higher than cyclobenzaprine concentrations observed in human plasma at therapeutic doses (mean peak concentration at steady state following the prescription dose of 10 mg every 8 hours was 0.083 μM). Based on this, cyclobenzaprine has very little potential for inhibition of cytochrome P-450-mediated reactions at therapeutic doses.

5.2 Human Metabolism

In humans, 50.8% of a radiolabeled cyclobenzaprine dose was recovered in urine and 13.5% of dose was recovered in feces after oral administration. Recovery was similar after intravenous administration (48.8% of dose in urine and 20.6% in feces). The major metabolites of cyclobenzaprine identified in human urine were a glucuronide conjugate (11 to 22%), *cis*-10,11-dihydroxynortriptyline (6 to 7%), *N*-desmethyl cyclobenzaprine (3%), and α-3-hydroxycyclobenzaprine (3 to 6%). Only minor amounts of unchanged drug were present in urine.

5.3 Pharmacokinetics

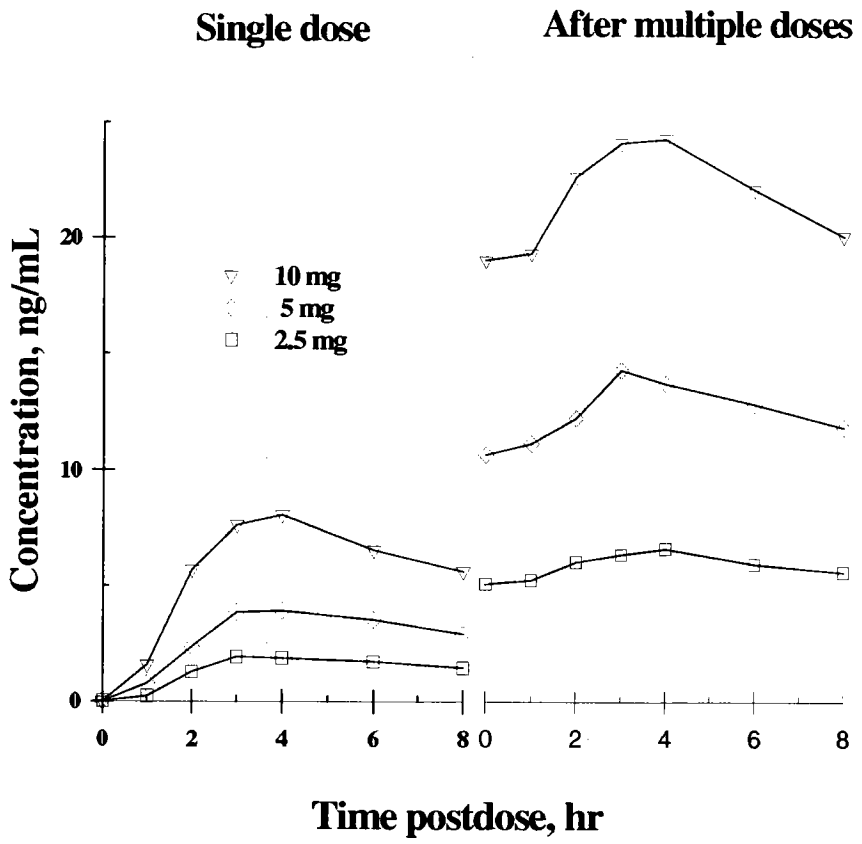
Mean (±SD) plasma clearance following intravenous administration of a 1.25 mg bolus dose was 689 (±216) mL/min. Plasma concentrations after I.V. bolus administration increased initially, peaking as much as 4 hours postdose, and then declined slowly. This unusual plasma concentration profile after I.V. administration has previously been observed for cyclobenzaprine in man as well as for total radioactivity in plasma after administration of radiolabeled cyclobenzaprine hydrochloride in man and laboratory animals. It is most likely attributable to rapid and extensive uptake of cyclobenzaprine by tissue.

The pharmacokinetics and dose proportionality of cyclobenzaprine were investigated after oral single and multiple doses of 2.5, 5, and 10 mg and mean plasma concentration profiles are shown in Figure 9. At each dose level, there was about fourfold accumulation of drug in plasma, and steady state was attained within 3 to 4 days after administration of cyclobenzaprine every 8 hours. Effective half-life at each dose level was about 18 hours. Plasma concentration increased proportionally to dose supporting the conclusion that cyclobenzaprine pharmacokinetics are linear over the dose range studied.

5.3 Pharmacokinetics (Cont.)

Figure 9

Cyclobenzaprine Mean Plasma Concentrations (0 to 8 hours) Over an 8-Hour Dosing Interval After a Single Oral Dose (Day 1) and After Dosing Every 8 Hours for 7 Days (n=18)



Bioavailability and bioequivalence were determined for two 5-mg tablet formulations of cyclobenzaprine hydrochloride. One tablet formulation, manufactured using a planetary mixing process, was used in clinical studies, and the other tablet formulation, manufactured using a high-shear mixing process, is the proposed market image. Mean systemic bioavailabilities (90% CI) of the two tablet formulations were both 0.55 (0.51, 0.60) and the formulations were bioequivalent.

5.3 Pharmacokinetics (Cont.)

Cyclobenzaprine was administered without regard to food in the clinical studies of safety and efficacy. In the multiple-dose pharmacokinetics studies, cyclobenzaprine was administered without regard to food, except it was administered in fasting subjects for doses following which concentration profiles were obtained. Given the long effective half-life (18 to 23 hours) and fourfold accumulation when dosed every 8 hours, the drug in the body at steady state is derived from several days of dosing. Therefore, steady-state pharmacokinetic parameters in these studies would largely reflect administration without regard to food. The effect of food on cyclobenzaprine pharmacokinetics was not formally studied because the clinical data support dosing without regard to food.

5.4 Pharmacokinetics in Different Subpopulations

Cyclobenzaprine is extensively metabolized, which raised the possibility that cyclobenzaprine pharmacokinetics may be substantially altered in the elderly (e.g., due to reduced liver mass) and in subjects with hepatic impairment. Therefore, the pharmacokinetics of cyclobenzaprine were studied in these subpopulations. The effect of gender on cyclobenzaprine pharmacokinetics was not formally studied, but was included in the statistical analysis of the 3 multiple-dose pharmacokinetics studies.

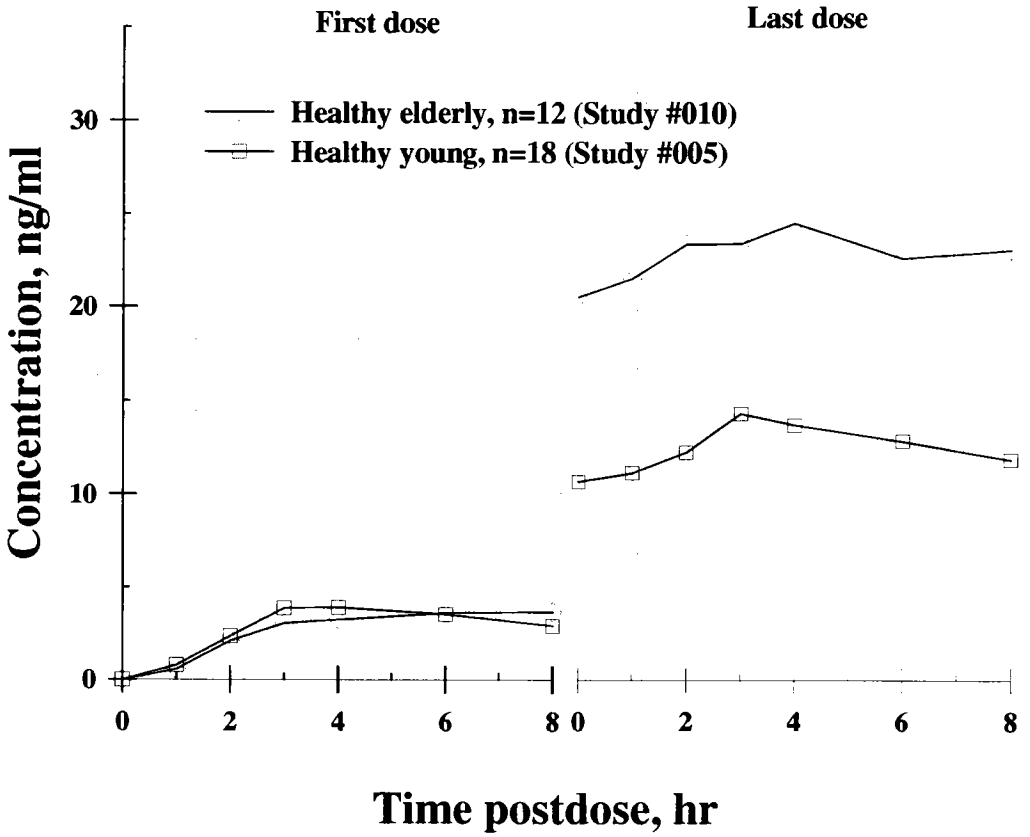
5.4.1 Effect of Age

The pharmacokinetics of cyclobenzaprine were investigated in elderly subjects (mean age: 71.3 years; range: 65 to 79 years; 6 males, 6 females) who received oral doses of 5-mg cyclobenzaprine hydrochloride tablets t.i.d. The results from this study were compared to those in healthy young subjects (mean age: 28.7 years; range: 22 to 40 years; 8 males, 10 females) receiving the same dosing regimen in a separate study. Mean plasma concentration profiles after the first and last doses in elderly and younger subjects are shown in Figure 10.

5.4.1 Effect of Age (Cont.)

Figure 10

Cyclobenzaprine Mean Plasma Concentrations in Healthy Elderly and Young Subjects After a Single Oral Dose of 5 mg and After Dosing 5 mg Every 8 Hours for 7 Days



After the first dose, cyclobenzaprine plasma concentration profiles were similar in elderly and young subjects. However, plasma concentrations after multiple dosing were significantly higher (1.8-fold for AUC and 1.7-fold for C_{max}) in the elderly subjects compared with the young subjects. This resulted from nearly 8-fold accumulation in the elderly versus 4.3-fold accumulation in the young. The difference at steady state can be attributed to a difference in effective half-life of cyclobenzaprine between elderly (mean 33.4 hours; range: 20.0 to 53.4 hours) and young (mean 18.4 hours; range: 9.3 to 41.3 hours) subjects. As a result of increased accumulation, steady-state concentrations in elderly subjects receiving 5 mg every 8 hours were in the same range as those previously observed in young subjects receiving the prescription dose of 10 mg every 8 hours.

5.4.1 Effect of Age (Cont.)

The basis for the differences in steady-state plasma concentrations of cyclobenzaprine between young and elderly is not known. One possible explanation for the increased accumulation in the elderly is reduced hepatic mass resulting in reduced metabolic clearance. The difference cannot be attributed to changes in renal function. Renal function was normal in the elderly subjects (creatinine clearance ranged from 67 to 101 mL/min) and subjects at the low end of this range did not show higher plasma levels of cyclobenzaprine.

5.4.2 Effect of Hepatic Insufficiency

The effect of hepatic insufficiency on cyclobenzaprine pharmacokinetics was investigated in a study comparing 16 subjects with mild-to-moderate hepatic insufficiency (11 males, 5 females) and 8 age-matched healthy subjects (5 males, 3 females). Hepatically impaired subjects in this study had a clinical diagnosis of hepatic insufficiency due to alcoholic liver disease based on a Pugh-Child classification of 5 to 11. Serum creatinine and BUN were required to be within 150% of normal range and creatinine clearance was required to be greater than 65 mL/min/1.73 M^2. Each subject received oral doses of 5-mg cyclobenzaprine hydrochloride tablets t.i.d. for 7 days and a final dose on the eighth day.

Statistical analysis of $AUC_{(0\text{-}8\ hr)}$ and C_{max} on Day 8 indicated a significant population (hepatic versus healthy)-by-gender interaction. This means that the effect of hepatic impairment was different in males compared to females in this study. Cyclobenzaprine plasma concentrations, after multiple dosing, were significantly higher for males with hepatic impairment compared with male controls, while no such differences were observed in females. However, healthy females in this study had much higher drug concentrations at steady state than previously observed in healthy young females. Plasma concentrations for hepatically impaired subjects receiving 5 mg every 8 hours are in the same range as healthy young subjects receiving the prescription dose of 10 mg every 8 hours.

Hepatically impaired subjects of both genders showed about eightfold accumulation of cyclobenzaprine in plasma over the course of the study as shown by geometric mean (90% CI) accumulation ratios (Day 8 $AUC_{(0\text{-}8\ hr)}$/ Day 1 $AUC_{(0\text{-}8\ hr)}$) of 8.0 (7.5, 8.4) and 8.4 (7.8, 9.0) for hepatically impaired males and females, respectively. Corresponding accumulation ratios for the age-matched control group of healthy males and females were 5.0 (4.2, 6.0) and 7.4 (5.5, 10.1), respectively. In an earlier study of healthy young subjects, there was approximately fourfold accumulation after dosing every 8 hours in both males and females. A comparison of accumulation between studies suggests that the population-by-gender interaction in the hepatic interaction study may be largely attributable to the higher accumulation observed in the healthy female

5.4.2 Effect of Hepatic Insufficiency (Cont.)

control group. Age is a likely explanation for this higher accumulation. The female controls were 10 years older, on average, than the male controls (mean ages 58.7 years in females versus 48.8 years in males) and were approaching the age of the subjects in the elderly study where higher accumulation was also observed. The small size of the female control group (n=3) may also have been a factor. Mean effective half-life was 46.2 hours (range: 22.4 to 188 hours) in hepatically impaired subjects and 23.1 hours (range: 10.7 to 51.2 hours) in control subjects.

While no definite conclusions regarding the effect of hepatic impairment can be drawn because of the confounding effects of age and gender, it appears that hepatic impairment increased steady-state plasma concentrations of cyclobenzaprine as the result of increased effective half-life, at least in males.

5.4.3 Effect of Gender

The effect of gender on cyclobenzaprine pharmacokinetics was not formally studied, but was included in the statistical analysis of the three multiple-dose pharmacokinetics studies. In the single-/multiple-dose pharmacokinetics study there were no statistically significant differences between males and females for any of the pharmacokinetic parameters analyzed. However, $AUC_{(0\text{-}8\ hr)}$ and C_{max} after the last dose (as well as accumulation rate constant) were marginally different between genders. These results suggest that there may have been slightly more accumulation in females; however, this study was not powered to detect a difference.

In the elderly, mean pharmacokinetic parameters at steady state were not significantly different in men and women, but there was an overall trend towards higher concentrations in men. The trend in the elderly was opposite to that observed in young subjects.

In the healthy control panel of the hepatic impairment study, steady-state plasma concentrations of cyclobenzaprine were significantly higher in females than males. The male/female geometric mean ratios (90% CI) at steady state were 0.33 (0.20, 0.57) for $AUC_{(0\text{-}8\ hr)}$ and 0.34 (0.21, 0.57) for C_{max}. However, these results can be attributed to the effect of age since, on average, the females were 10 years older than the males.

Taken together, results of the three multiple-dose pharmacokinetics studies suggest that steady-state plasma concentrations of cyclobenzaprine may be different in males and females; however, the magnitude of any difference appears to be relatively small.

5.5 Drug-Drug Interactions

Cyclobenzaprine is subject to both oxidation and conjugation, forming numerous metabolites. Oxidation to form *N*-desmethyl cyclobenzaprine has been shown to be mediated primarily by cytochrome P-450s 3A4 and 1A2 with 2D6 having a minor role. This multiplicity of metabolites and pathways indicates that cyclobenzaprine pharmacokinetics are not likely to be affected by drugs that specifically inhibit individual cytochrome P-450 enzymes. In vitro studies have also shown that cyclobenzaprine at clinically relevant concentrations has little potential to inhibit the cytochrome P-450 system and, therefore, the pharmacokinetics of other drugs.

Pharmacokinetic drug-drug interaction studies conducted to support previous applications have shown no clinically significant interaction between cyclobenzaprine and either aspirin or diflunisal. Anecdotal data from the hepatic impairment and elderly studies suggest that acetaminophen does not substantially alter cyclobenzaprine pharmacokinetics. No reports of pharmacokinetic drug-drug interactions involving cyclobenzaprine have been identified in the literature despite extensive market experience at the prescription strength of 10 mg. Based on these observations, cyclobenzaprine has little potential for clinically significant pharmacokinetic drug-drug interactions.

Several potential pharmacodynamic interactions are identified in the product circular for cyclobenzaprine hydrochloride 10-mg tablets. Cyclobenzaprine may interact with MAO inhibitors. Hyperpyretic crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs. Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. These effects may also occur with cyclobenzaprine, which is structurally similar to tricyclic antidepressants.

It also has been reported that the risk of seizures in patients taking the analgesic tramadol is increased with concomitant administration of tricyclic antidepressants. This pharmacodynamic interaction likely reflects a reduction of the seizure threshold by the tricyclic compound. A published report indicates that seizures have been reported in 4 patients who took cyclobenzaprine and tramadol concomitantly. Based on this information, the proposed OTC label warns against concomitant use of cyclobenzaprine and tramadol.

5.6 Clinical Pharmacology Conclusions

1. Cyclobenzaprine *N*-demethylation is mediated primarily via cytochrome P-450s 3A4 and 1A2, while cytochrome P-450 2D6 plays a minor role.

2. Cyclobenzaprine has very little potential for inhibition of cytochrome P-450-mediated reactions at clinically relevant concentrations based on the relatively high *Ki* values obtained for human liver microsomes.

3. Plasma concentrations increase proportionally to dose over the dose range 2.5 to 10 mg, indicating the pharmacokinetics of cyclobenzaprine are linear over this dose range.

4. There is approximately fourfold accumulation of cyclobenzaprine in plasma when dosed every 8 hours.

5. Plasma clearance of cyclobenzaprine is 689 mL/min.

6. The bioavailability of cyclobenzaprine hydrochloride 5-mg tablets is 0.55.

7. Cyclobenzaprine hydrochloride 5-mg tablets manufactured by a high-shear process (proposed for marketing) are bioequivalent to cyclobenzaprine hydrochloride 5-mg tablets manufactured by a planetary process (used in most clinical studies).

8. Steady-state plasma concentrations of cyclobenzaprine are increased in the elderly as the result of increased effective half-life.

9. Mild-to-moderate hepatic impairment increases steady-state plasma concentrations of cyclobenzaprine as the result of increased effective half-life, at least in males.

10. The magnitude of any differences in steady-state plasma concentrations of cyclobenzaprine between males and females is relatively small.

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LABEL DEVELOPMENT

6. Label Development

The proposed nonprescription label is presented in Attachment 1. The components include the back panel of the carton and the package insert. The development of this draft label is outlined below.

The first draft label was provided to participants in the Pattern-of-Use study (Protocol 009) and included directions closely matching the treatment regimen in the double-blind efficacy trials (Protocols 006 and 008). Based on the results of that study and the pharmacokinetic data in the elderly, the duration of treatment was increased to 10 days and a geriatric warning was added. The label was also reformatted to be consistent with FDA's Proposed Rule on OTC Drug Labeling.

Drafts of the proposed label were discussed with FDA on two occasions. As a result of Agency comments, the following revisions were made and appear in the current proposal:

- Minimum age of 18 years
- Prescription circular warnings explained in consumer-friendly language
- Insert includes non-pharmacologic advice for treatment of back pain
- Outer carton includes description of time to effect

6.1 Rationale for Information in Label

Indication

The proposed indication for nonprescription cyclobenzaprine is relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury. This is the condition that was studied in the nonprescription trials, and is consistent with the current indication for the prescription dose.

Dose

The proposed nonprescription dose is 5 mg three times a day (t.i.d.), which is half of the current prescription dose. The placebo-controlled Phase III trials (Protocols 006 and 008) evaluated 3 different doses: 10, 5, and 2.5 mg, each given t.i.d. The 10- and 5-mg doses were both significantly better than placebo in all primary parameters by the end of 7 days treatment. The only apparent efficacy difference between cyclobenzaprine 10 mg and cyclobenzaprine 5 mg is that the higher dose has a faster onset of effect. Daily Relief from Starting Backache ratings showed that onset of effect with cyclobenzaprine 10 mg appeared to occur within the first 2 doses on Day 1. The same ratings showed that onset

6.1 Rationale for Information in Label (Cont.)

of effect with cyclobenzaprine 5 mg occurred 24 to 48 hours after the first dose. The incidence of somnolence in placebo-controlled Phase III studies, however, is appreciably lower with cyclobenzaprine 5 mg (29%) compared to cyclobenzaprine 10 mg (38%). The 2.5-mg dose was evaluated in 1 study and was found to be suboptimal as it achieved statistical significance compared to placebo in only one of the three primary parameters. Based on the efficacy and safety profiles of the various cyclobenzaprine dosages, the 5-g t.i.d. dose appears to have the most favorable benefit/risk ratio for self-medication.

Patients were instructed to use study medication for 7 days in Protocols 006 and 008. Approximately 25% of patients receiving cyclobenzaprine 5 mg in those trials still had moderate or greater muscle spasm after 7 days of treatment. In the Pattern-of-Use study, patients were provided with 30 tablets and a label that instructed them to "take 1 tablet every 6 to 8 hours, do not take continuously for more than 7 days". Approximately half the patients (57%) used medication for 7 to 9 days. Ninety-two percent of patients took study medication for 10 days or less. Taken together, the 3 studies indicate that many patients may benefit from 7 to 10 days of medication. This is not unexpected given the natural history of acute back pain [4] and the current prescription label, which recommends treatment for up to 14 days. The proposed nonprescription label instructs patients not to medicate for longer than 10 consecutive days unless directed by a physician. This is consistent with the maximum duration of treatment for nonprescription ibuprofen products, which also may be used to treat acute back pain.

Warnings About Drug Interactions

Concomitant use of cyclobenzaprine and a monoamine oxidase inhibitor (MAOI) can produce serious toxicity. The proposed label addresses this contraindication by including a warning not to use cyclobenzaprine if the patient is taking a MAOI or within 14 days after its discontinuation. Similar MAOI warnings are included in cough/cold products containing pseudoephedrine. Since the risk of seizures may be increased when cyclobenzaprine is used with tramadol, the label includes a warning against such use. A similar warning already exists in the tramadol label. Concomitant use of sedatives, tranquilizers, antidepressants, and other muscle relaxants may produce increased sedation, and an appropriate warning is included in the proposed label. Patients are advised to avoid alcohol while taking cyclobenzaprine since concomitant use can lead to increased drowsiness.

The prescription circular includes a precaution about use by patients taking anticholinergic medications. Dry mouth is the most common anticholinergic effect of cyclobenzaprine, and it is dose related. An increased risk of dry mouth is not a serious clinical consequence. The clinical concern underlying the precaution is that patients taking both cyclobenzaprine and an anticholinergic drug could have an increased risk of

6.1 Rationale for Information in Label (Cont.)

urinary retention or angle-closure glaucoma. It is reasonable to expect the risk with the 5-mg nonprescription dose of cyclobenzaprine to be lower than with the 10-mg prescription dose. Since many drugs (e.g., antihistamines) can have anticholinergic properties, a precaution advising against use of anticholinergic drugs, or drugs with anticholinergic properties, is impractical and difficult to communicate in consumer-friendly terms. Instead, the proposed nonprescription cyclobenzaprine label advises people with a history of glaucoma or difficulty urinating to consult their physician before using cyclobenzaprine.

There are no apparent drug interactions between cyclobenzaprine and acetaminophen or nonsteroidal anti-inflammatory drugs. Concomitant use of ibuprofen, acetaminophen, or aspirin did not appear to affect the tolerability of cyclobenzaprine in the nonprescription studies. A pharmacokinetic interaction study with aspirin revealed no interaction. Based on the heterogeneous metabolism of cyclobenzaprine within the cytochrome P450 system, pharmacokinetic interaction with other P450-metabolized drugs is unlikely. It is estimated that 72% of cyclobenzaprine prescriptions are accompanied by a prescription for an analgesic. Since cyclobenzaprine 5 mg does not provide immediate relief, patients may benefit from also using nonprescription analgesics that could provide partial temporary relief.

Warnings About Preexisting Conditions

The current prescription circular includes the following contraindications to the use of cyclobenzaprine: hypersensitivity to the drug, acute recovery phase of myocardial infarction, arrhythmias, heart block or conduction disturbances, congestive heart failure, hyperthyroidism. The prescription circular includes precautions about use by patients with a history of urinary retention, angle-closure glaucoma, and increased intraocular pressure. The proposed nonprescription label includes warnings in "consumer-friendly" language advising patients to ask a doctor before using cyclobenzaprine if they have heart disease, thyroid disease, glaucoma, or difficulty urinating. Warnings of this type are common in OTC labels and understood by consumers. They are also advised not to use the drug if they are allergic to cyclobenzaprine. Clearance of cyclobenzaprine may be reduced in patients with hepatic insufficiency. Therefore, the proposed label instructs patients with liver disease to ask their physician before using cyclobenzaprine.

The clearance of cyclobenzaprine is reduced in elderly patients. Therefore, the proposed nonprescription label advises patients 65 years of age or older to ask their physician before using cyclobenzaprine.

The efficacy of cyclobenzaprine in children has not been established. Assessment and treatment of back pain in children less than 18 years old may be quite different than for adults. Therefore, the proposed nonprescription label advises that the product not be used by patients less than 18 years old unless directed by a physician.

6.1 Rationale for Information in Label (Cont.)

Certain symptoms may indicate that acute back pain is due to a serious underlying condition such as infection, neoplasm, or nerve compression [4]. While the risk of adverse experiences due to cyclobenzaprine may not be increased by the presence of these conditions, any delay in obtaining definitive evaluation and treatment should be avoided. Therefore, the proposed label advises patients to consult a physician if they have fever, weight loss, weakness in an arm or leg, pain shooting down the legs, or pain that gets worse when they lie down.

6.2 Label Comprehension Study

This study was conducted to test consumer comprehension of the uses, directions and warnings associated with nonprescription cyclobenzaprine as presented on the revised label. Mall-intercept interviews were conducted in 14 geographically dispersed locations across the continental United States. The interviews were conducted among a representative sample of 400 adults aged 18+ with gender and age quotas established to reflect the adult population in the United States. The mean age of respondents in the representative sample was 43 years. The majority were single and at least high school graduates. The mean and median annual household income were $42,198 and $32,075, respectively. Eighty percent reported they had ever suffered from back or neck pain, 63% said they had suffered from back or neck pain in the past 12 months, and 37% indicated that they had previously taken a muscle relaxant.

Respondents saw a picture of the front of the package and the back label, read them, and answered a questionnaire administered by an interviewer. The picture of the package and the back label were available for the respondents to refer to at any time during the interview. It was hypothesized that at least 80% of respondents would understand the indication, directions, and key warnings after reading the back panel. Respondents then read the package insert and were requestioned about earlier answers that were incorrect.

Table 50 shows the results for the questions about the appropriate uses for the product. Ninety-four percent of respondents understood that it is appropriate to use the product for back or neck pain due to muscle strain, overuse, or minor injury. The table also shows that 19, 34, 23, and 14% of respondents mistakenly thought that it is appropriate to use the product for headaches (76/400), leg cramps (137/400), arthritis in the knees (91/400), and menstrual cramps (29/201) respectively. The percentage of respondents who indicated that the product is appropriate for the back and neck areas exceeds the reported 80% stated in the evaluation criteria. The percentage of respondents who indicated that the product was appropriate is more than the 20% maximum stated in the evaluation criteria for leg cramps and arthritis in the knees.

6.2 Label Comprehension Study (Cont.)

Table 50

Label Comprehension Study: Conditions for Which Use of Cyclobenzaprine is Judged Appropriate After Reading Label—Percent of Respondents

Number of Respondents Per Group:	Total N=400	Age 18 to 64 N=354	Age 65+† N=102	Education Level Less Than H.S. Grad† N=48	Education Level H.S. Grad + N=362
	A	B	C	D	E
Back or neck pain due to recent muscle strain	96	96*	89	94	97
Back or neck pain due to recent muscle overuse	94	94	92	98*	94
Painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury	94	94*	85	92	94
Leg cramps	34	34	39	33	35
Arthritis in the knees	23	22*	31	25	23
Headaches	19	18	25	23	19
Menstrual cramps‡	14	14	10	22	13

†Includes sample augment.
‡Asked among women only.
*Significant difference (90% CI) for Column B versus C or Column D versus E.

To help satisfy concerns regarding comprehension level and reading skill, the representative sample was augmented to obtain 102 consumers 65+ years of age (46 in representative sample and 66 additional people) and 48 consumers with less than a high school education (38 in representative sample and 10 additional people). Although still reaching higher than 80%, consumers aged 65+ were significantly less likely to state that cyclobenzaprine was appropriate for back or neck pain due to recent muscle strain and painful muscle tightness and spasm due to recent strain, overuse, or minor injury. This elderly group was significantly more likely to state that the product was appropriate for arthritis in the knees.

6.2 Label Comprehension Study (Cont.)

Table 51 shows the results for questions regarding the directions for use. Ninety-one percent of respondents understood that only 1 tablet should be taken at a time (365/400). Ninety-three percent of respondents understood that 3 tablets at most should be taken in a 24-hour period (371/400). Eighty-eight percent of respondents (351/400) understood that the product may be used for 10 days in a row. The percentage of respondents who indicated the correct answers exceed the 80% stated in the evaluation criteria. Responses did not differ significantly between consumers aged 65+ and those younger than 65, or between those with less than a high school education and those with 12 years or more of school.

Table 51

Label Comprehension Study: Interpretation of Dosing Instructions After Reading Label—Percent of Respondents

		Age		Education Level	
	Total	18 to 64	65+†	Less Than H.S. Grad†	H.S. Grad +
Number of Respondents Per Group:	N=400	N=354	N=102	N=48	N=362
	A	B	C	D	E
Max. tablets per dose					
1	91	91	90	96	91
2	9	9	8	4	9
Unspecified	<0.5	<0.5	2	0	<0.5
Max. tablets per day					
1	0	0	1	0	0
2	5	5*	2	4	5
3	88	88	84	92	88
4 or more	7	7	11	4	7
Unspecified	1	<0.5	2	0	1
Maximum Days in Row					
1 to 4	5	5	3	4	5
5 to 9	4	4	5	4	4
10	88	88	89	88	88
11 to 14	2	2	1	2	2
15 or more	1	1	0	0	1
Unspecified	1	1	2	2	1

† Includes sample augment.
* Significant difference (90% CI) Column B versus C.

6.2 Label Comprehension Study (Cont.)

Table 52 summarizes the results for questions about conditions indicated on the label for which a doctor should be consulted before using the product. The proportion of respondents correctly answering each question exceeded the 80% stated in the evaluation criteria. Responses generally did not differ significantly among consumers aged 65+ or with less than a high school education. The one exception was that people aged 65+ were more likely to understand the warning about difficulty urinating.

Table 52

Conditions For Which a Doctor Should Be Consulted
Before Using Cyclobenzaprine: Percent of Respondents

		Age		Education Level	
	Total	18 to 64	65+†	Less Than H.S. Grad†	H.S. Grad +
Number of Respondents Per Group:	N=400	N=354	N=102	N=48	N=362
	A	B	C	D	E
If Someone Has . . .					
Heart, liver, or thyroid disease	95	94	95	92	96
Pain shooting down their legs or back pain that gets worse when they lie down	93	92	91	96	93
Weakness in an arm or leg	88	88	87	92	87
Fever	81	80	79	81	81
Difficulty urinating	80	79*	89	73	81
If Someone is . . .					
Taking sedatives, tranquilizers, antidepressants, or other muscle relaxants	95	94	92	94	95
65 years of age or older	92	92	90	94	92

†Includes sample augment.
*Significant difference (90% CI) for Column B versus C.

6.2 Label Comprehension Study (Cont.)

Table 53 shows the results of questions about sedation caused by use of the product which were described on the label. Ninety-eight percent (392/400) of respondents understood that significant drowsiness may occur when using the product. The related warnings about driving and concomitant alcohol or medications were similarly well understood. The percentage of respondents who answered correctly exceeded the 80% stated in the evaluation criteria. Responses did not differ significantly among consumers with less than a high school education. Although consumers age 65+ were significantly less likely to understand that significant drowsiness may occur when using the product, 92% (94/102) of this age group understood the warning.

Table 53

What Label Says About Drowsiness: Percent of Respondents

		Age		Education Level	
	Total	18 to 64	65+†	Less Than H.S. Grad†	H.S. Grad +
Number of Respondents Per Group:	N=400	N=354	N=102	N=48	N=362
	A	B	C	D	E
Significant drowsiness may occur	98	98*	92	96	98
Avoid alcoholic beverages	97	96	95	92	97
Use caution when driving a motor vehicle or operating machinery	96	96	96	96	96
Alcohol, sedatives, and tranquilizers increase the drowsiness effect	96	96	92	92	97

†Includes sample augment.
*Significant difference (90% CI) for Column B versus C.

The package insert tended to improve understanding of the conditions for which the product was and was not appropriate. Among those respondents who indicated that the product was for headaches, leg cramps, arthritis in the knees, or menstrual cramps after reading the label alone, 33% (28/86), 31% (43/138), 36% (36/99), and 42% (14/33) indicated that the product was inappropriate for these conditions respectively after reading the package insert.

6.2 Label Comprehension Study (Cont.)

Table 54 shows that after reading the insert, only 14% (57/400) of the representative sample felt this product could be used for arthritis in the knees, versus 23% (91/400) after reading the label alone. The proportion who thought the product could be used for leg cramps also declined from 34% to 23%. The insert stated that cyclobenzaprine should not be used for leg cramps, but there was no mention of the other three conditions. The realization that those unspecified conditions were not appropriate indicates that respondents had an improved understanding of the product after reading the insert.

Table 54

Conditions for Which Use of Cyclobenzaprine is Appropriate, Pre- Versus Post-Insert for Inappropriate Conditions: Percent of Respondents

Number of Respondents per Group:	Total N=400		65+† N=102		Less than H.S. Grad† N=48	
	Label Only	Label + Insert	Label Only	Label + Insert	Label Only	Label + Insert
	A	B	C	D	E	F
Leg cramps	34*	23	39	28	33	25
Arthritis in the knees	23*	14	31	24	25	19
Headaches	19*	13	25	18	23	17
Menstrual cramps‡	14	10	9	8	22	22

† Includes sample augment.
‡ Asked among women only.
* Significant difference (90% CI) for Column A versus B.

The package insert helped consumers understand that the product works differently than pain relievers. After reading the back panel, 70% (281/400) of respondents understood that the product works differently than pain relievers. Among the 30% of respondents who indicated that the product works the same as pain relievers after reading the back panel alone, 59% (70/119) indicated that the product works differently than pain relievers after reading the insert.

In summary, consumer comprehension was high for most of the key elements, including appropriate use for back and neck pain, dosing, length of use, warnings and side effects associated with cyclobenzaprine. It is noteworthy that 98% of the representative sample understood that the product could cause drowsiness. It is also reassuring that 95% of the representative sample understood that concomitant use of certain drugs should be avoided.

6.2 Label Comprehension Study (Cont.)

Based on the results of this study, the font of the back panel text was increased to make it easier to read, especially for those 65+. The insert was also augmented to explain why those 65+ should talk with their doctors before starting to take cyclobenzaprine. Text was also added to explain how the product works, which should help consumers determine which conditions are not appropriate. A statement was added that the product is not effective for leg cramps.

Conclusions:

- The key elements of the label were well understood among a representative sample of consumers.

- The insert tended to improve comprehension of appropriate uses and difference from analgesics.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

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BENEFIT VERSUS RISKS

7. Benefits Versus Risks Relationship

Acute back pain is an extremely common condition [4]. Up to 75% of adults report back problems at some time in their lives and the condition tends to recur [18]. Nonprescription analgesics and anti-inflammatory drugs are commonly used to treat acute back pain, but these agents do not provide adequate relief for everyone. Since 1977, physicians have prescribed cyclobenzaprine 10 mg as an adjunct to rest, physical therapy, and analgesics for patients seeking relief of muscle spasm associated with acute back or neck pain. Drowsiness, however, is a common side effect with the 10-mg dose. Therefore, studies were conducted to investigate whether a lower, and presumably less-sedating, dose would provide effective relief. Studies were also done to assess the effects of the proposed nonprescription dose on psychomotor function.

7.1 Potential Benefits of Nonprescription Cyclobenzaprine

Two well-controlled clinical trials (Protocols 006 and 008) demonstrated the efficacy of cyclobenzaprine 5 mg. In these trials, cyclobenzaprine 5 mg administered t.i.d. for 7 days was clinically and statistically significantly more effective than placebo in patients with acute back or neck pain. The primary endpoints were patient ratings of medication helpfulness, global impression of change, and relief from starting backache. In both studies, the proportion of patients considered "responders" in the primary endpoints was 11 to 20 percentage points greater in the cyclobenzaprine 5-mg group than in the placebo group. Differences of that size are clearly clinically meaningful. The calculated effect sizes also compare favorably with those for famotidine 10 mg and OTC antihistamines, nonprescription medications approved for conditions that rely on subjective self-assessment of symptoms.

The efficacy of cyclobenzaprine 5 mg t.i.d. was evident to the physicians as well as the patients. Physician assessments performed at baseline and subsequent visits confirmed that cyclobenzaprine 5 mg was associated with a greater reduction in palpable paraspinal muscle spasm compared to placebo. This finding on physical examination in both placebo-controlled trials further validates the subjective ratings provided by the patients. This finding also provides evidence that cyclobenzaprine 5 mg acts as a "muscle relaxant."

Protocol 006 showed that the efficacy of the 5-mg dose was generally similar to that of the already approved 10-mg prescription dose. There was evidence for a faster onset of action, and increased incidence of somnolence, with the 10-mg dose. Cyclobenzaprine 5 mg t.i.d. was effective within 24 to 48 hours of initiating treatment. The short lag before onset of efficacy did not appear to reduce overall patient satisfaction with cyclobenzaprine 5 mg, as global ratings after 7 days of treatment were similar to those with 10 mg. Concomitant use of analgesics was prohibited in the pivotal trials, but there is no medical reason why patients could not use analgesics in addition to cyclobenzaprine, if needed for relief during the first day or 2 of treatment.

7.1 Potential Benefits of Nonprescription Cyclobenzaprine (Cont.)

It had previously been shown that the efficacy of cyclobenzaprine 10 mg is not dependent on the presence of sedation. The nonprescription studies reported here have extended that finding to cyclobenzaprine 5 mg. A combined analysis of the placebo-controlled trials demonstrated the efficacy of cyclobenzaprine 5 mg t.i.d. in the subgroup of patients not reporting sedation. This is consistent with the observation that cyclobenzaprine 5 mg can have similar efficacy but less potential for sedation than cyclobenzaprine 10 mg.

In most patients, acute musculoskeletal spasm tends to resolve over time. An effective treatment should hasten the resolution of the spasm and pain. The 2 pivotal studies showed that relief occurred more quickly with cyclobenzaprine 5 mg t.i.d. than with placebo. The median Time-to-A Lot or Complete Relief was approximately 2 days less for cyclobenzaprine 5 mg than placebo. To the extent that patients need to restrict their activities because of their pain and spasm, earlier relief should allow patients to resume their normal activities sooner.

Acute painful muscle spasm of the back and neck is a highly prevalent condition among adults in their 30s and 40s and a major contributor to morbidity and lost productivity in this society. With greater access to cyclobenzaprine, without the cost and inconvenience of a physician visit, many people could be effectively treated who might not be adequately treated with OTC analgesic products only. Reducing the period of morbidity by 1 to 2 days could yield a large cumulative benefit to individual patients (quality of life and wages) and society as a whole (productivity and direct health-care costs). Having an effective OTC product available represents an important option to consumers seeking to self-treat a commonly occurring, self-recognizable condition.

7.2 Potential Risks of Nonprescription Cyclobenzaprine

The safety profile of cyclobenzaprine has been well characterized in clinical trials and through postmarketing surveillance. The substantial marketing experience with cyclobenzaprine 10 mg also provides information about the margin of safety with cyclobenzaprine 5-mg tablets.

7.2.1 Risks Related to Sedation

The most common adverse experience with cyclobenzaprine is somnolence, and that effect is dose related between 2.5 mg and 10 mg t.i.d.. Somnolence was reported by 29% of patients who received cyclobenzaprine 5 mg t.i.d. in the placebo-controlled Phase III studies (compared to 38% who received cyclobenzaprine 10 mg t.i.d., and 10% who received placebo). Somnolence usually began within 2 days of initiating treatment with cyclobenzaprine 5 mg, and the somnolence was generally described as mild or moderate. Only 2.6% of patients receiving cyclobenzaprine 5 mg reported severe somnolence. Somnolence generally did not increase further with continued dosing. Some patients reported that somnolence resolved while they continued the medication, suggesting that adaptation occurs.

7.2.1 Risks Related to Sedation (Cont.)

The degree of sedation associated with cyclobenzaprine 5 mg was assessed in the 6 psychomotor studies and compared to that of nonprescription antihistamines (diphenhydramine 50 mg, clemastine 1 mg) also known to have sedative properties. The studies showed that the peak magnitude of the subjective feeling of drowsiness was similar between cyclobenzaprine 5 mg and the two nonprescription antihistamines. The time to peak sedation differed among the tested drugs, corresponding to their pharmacokinetic profiles.

While the studies showed subjective drowsiness with cyclobenzaprine 5 mg, there was no consistent pattern of impairment of psychomotor function with cyclobenzaprine as measured by computerized test batteries, including 2 studies validated to assess driving-related skills under conditions of drug- or alcohol-induced impairment. Protocols 014 and 015 showed that subjects receiving cyclobenzaprine 5 mg were generally able to perform driving-related skills adequately during the time of peak sedation despite reporting a sense of drowsiness. Performance with multiple doses of cyclobenzaprine 5 mg was not worse than with a single dose of diphenhydramine 50. The consistent impairment observed with amitriptyline 50 mg served to validate the psychomotor tests employed—tests which failed to show functional impairment with cyclobenzaprine 5 mg t.i.d.

Products are determined to be safe for OTC use if their risks can be adequately managed by labeling. In the case of sedating nonprescription products, ample precedent exists with diphenhydramine and clemastine, which are both approved for OTC sale in the United States. There are numerous nonprescription products which contain diphenhydramine and have labels that warn of the potential for drowsiness. It is reasonable to conclude from the data presented in this application that the risks due to sedation with cyclobenzaprine 5 mg t.i.d. OTC would be no greater than those with some currently available nonprescription products, and less than with certain chronically administered prescription products, such as amitriptyline. The precedent with sedating antihistamines indicates that the risk associated with cyclobenzaprine-induced sedation can be managed with appropriate label warnings.

7.2.2 Risks of Neuropsychiatric Adverse Experiences Other Than Sedation

A postmarketing surveillance study with 6,311 patients published in 1980 solicited occurrences of hallucination associated with the prescription dose of cyclobenzaprine. These were found in 13 cases, yielding an incidence of 0.2%. The spontaneous reports of hallucination total 80 in the WAES database. As detailed in Section 3.3, many of these were elderly patients and the disturbance was apparently reversible. Based on the well-known association of psychiatric disturbance with atropine-like drugs [6], it is postulated that this effect is the result of the antimuscarinic pharmacology of the drug.

7.2.2 Risks of Neuropsychiatric Adverse Experiences Other Than Sedation (Cont.)

Since the anticholinergic effect of dry mouth is clearly dose related in the clinical study data, it is hypothesized that the psychiatric effect is similarly related to plasma drug concentrations. There were no reports of hallucinations with cyclobenzaprine 5 mg in the Nonprescription Cyclobenzaprine Clinical Studies. While the risk of hallucination cannot be eliminated by OTC labeling, it is not prohibitive to OTC use because it is likely to be quite rare, dose related, and reversible. The risk should be even lower with the OTC dose than the prescription dose given the 50% reduction in dose.

7.2.3 Risks Related to Anticholinergic Properties

Cyclobenzaprine has some anticholinergic properties. In the Nonprescription Cyclobenzaprine Clinical Studies, the second most common adverse experience with cyclobenzaprine 5 mg was dry mouth. This is an easily tolerated, dose-related symptom of little clinical import other than as evidence of the anticholinergic property of the drug. Other potential antimuscarinic effects include tachycardia, blurred vision, urinary retention, and an increase in intraocular pressure. These effects have not been commonly reported with marketed use of cyclobenzaprine 10 mg. The risk of these events occurring with cyclobenzaprine 5 mg should be reduced by advising patients who have a history of heart disease, urinary retention, or glaucoma to consult a physician before using the product.

7.2.4 Risks Related to Drug Interactions

Potential drug interactions with cyclobenzaprine include additive sedation with other sedating products or alcohol. Additionally, concomitant use with MAO inhibitors may produce serious toxicity. Warnings of both of these types are familiar to consumers of OTC drug products (e.g., sympathomimetics in cough-cold preparations). The proposed OTC label also warns against use with the prescription pain reliever tramadol, as there may be an increased risk of seizures when tramadol is used concomitantly with tricyclic compounds, including cyclobenzaprine. In vitro data show that cyclobenzaprine has very little potential for inhibition of cytochrome P-450-mediated reactions at therapeutic doses. The heterogeneity of metabolic pathways for cyclobenzaprine makes it unlikely that there would be a clinically meaningful interaction with other drugs that are inhibitors of a specific cytochrome P-450 enzyme. Thus, the potential for drug interactions can be managed by labeling, and is not a prohibitive issue in the evaluation of cyclobenzaprine for OTC use.

7.2.5 Risks of Abuse/Misuse

The risks of cyclobenzaprine being abused or misused are small. Cyclobenzaprine has not been reported to produce euphoria or other desired psychoactive effects, and therefore has no identifiable abuse potential. Data from the Drug Abuse Warning Network (DAWN) show that there is no pattern of widespread recreational use of cyclobenzaprine.

7.2.5 Risks of Abuse/Misuse (Cont.)

There is extensive information about overdoses of cyclobenzaprine. Sedation and sinus tachycardia are the most common manifestations. Serious cardiovascular effects are rare and occur substantially less often than with overdoses of tricyclic antidepressants. Fatality is very rare (0.02% of the nearly 17,000 single-agent ingestions reported to the poison control centers), and the therapeutic margin is fairly wide.

Use of the product for painful conditions other than acute back or neck pain is unlikely to have clinical consequences other than a lack of effectiveness. The likelihood of off-label use can be minimized by clear labeling. The proposed nonprescription package will include an insert that provides additional information about conditions for which use of cyclobenzaprine is inappropriate (e.g., leg cramps).

Acute back pain is a self-recognizable condition, and self-medication is medically appropriate for initial treatment. A published review of cases presenting as "acute back pain" is reassuring in that the chance of a serious underlying condition is small, as are the consequences of a brief delay in diagnosis [18]. The risk of misdiagnosis can be minimized by advising discontinuation after 10 days for back pain that worsens or does not improve. This recommendation is consistent with the current labeling for nonprescription ibuprofen products. The Pattern-of-Use study showed that most patients will comply with the dosing directions when allowed to self-medicate with cyclobenzaprine. The proposed nonprescription cyclobenzaprine label includes additional warnings about signs of infection or nerve entrapment. This additional information should further reduce the potential for inappropriate self-medication.

7.2.6 Risks Related to Age

Pharmacokinetic data show that steady-state plasma concentrations of cyclobenzaprine are increased in the elderly as the result of increased effective half-life. This increased accumulation of drug results in an effective doubling of the dose compared to young subjects after a week of treatment. While 2 psychomotor studies suggest that the elderly are less apt to experience sedation with cyclobenzaprine 5 mg t.i.d. than younger adults, some did nonetheless report somnolence in the Phase III trials. The dose-related anticholinergic properties of cyclobenzaprine could be bothersome to some elderly patients. An additional distinction related to advancing age is an increase in risk, albeit small, that the acute back pain is a symptom of a serious underlying condition. The low risks of an underlying neoplasm or a compression fracture are somewhat greater in elderly patients. Given these considerations, have added a warning to the proposed label directing those 65 years of age and over to consult their doctor before using nonprescription cyclobenzaprine.

7.3 Benefit-to-Risk Conclusions

Acute back pain is a highly prevalent condition that represents the second most common reason for an office visit to a primary care physician [16]. The large number of physician visits indicates the limited effectiveness of currently available nonprescription treatments. The category of muscle relaxant is available for open-shelf, nonprescription use in Canada. This supports the acceptability of such treatment without physician involvement.

Many people who now self-medicate with nonspecific analgesics for symptomatic relief of acute painful muscle spasm of the back could benefit from the substantial efficacy provided by cyclobenzaprine. A foreshortening of the clinical course with this product could curtail suffering, boost productivity, and permit early mobilization which could provide an additional benefit in tending to prevent progression to chronicity.

The sedative property of cyclobenzaprine should not preclude OTC availability. Somnolence, which is reported in about a third of people in clinical trials at the 5-mg t.i.d. dose, has been shown to be generally mild, comparable in degree to that of existing OTC products and unlikely to substantially impair psychomotor performance. While sedation and efficacy are independent effects, sedation appearing early in treatment may be useful to those whose back pain interferes with sleep. Clear labeling can warn consumers of the risk of drowsiness, guide against inappropriate use for conditions other than the intended or with prohibited drugs, differentiate from OTC analgesics, and direct people to their physicians for treatment as needed.

In conclusion, the risks of nonprescription treatment with cyclobenzaprine 5 mg can largely be managed by optimal labeling and do not outweigh the benefits of this effective adjunctive treatment option. Expanding access to this treatment option beyond the standard prescription avenue would enable consumers to self-treat this common condition in a more efficient manner.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

APPENDIX 1: PERFORMANCE TEST DESCRIPTION

APPENDIX 1

Descriptions of Performance Tests in Psychomotor Studies

Performance Tests in Studies 001, 002, 003, and 012

Most of the cognitive testing was undertaken using a color touchscreen linked to an IBM PC.

Wilkins auditory sustained attention. In this procedure the subject was required to listen to trains of auditory "beeps" from the computer. At the end of each train the subject was asked to indicate the number of beeps. Trains varied in length from 5-14 and were given in a random order. The beeps in a train had a duration of 50 msec and were separated by a random interval of 2-6 sec. Two blocks of trials, each lasting approximately 10 min. and separated by 30 min. of other cognitive tests, were run. The total number of errors made by the subject was recorded.

Visual sustained attention. Digits were presented one at a time for 100 msec. on the computer screen, at a rate of 40 per 2 min. for 10 min. against a random visual noise background. The subject was required to press a button whenever the target digit (3) appeared. In each 2 min. block of 40 trials there were 10 targets and 30 nontargets, chosen from the remaining digits 0-9. The interval between stimuli varied pseudorandomly between 900 and 4,900 msec (i.e., in each 40 trial block there were eight randomly placed occurrences of the following five interstimulus intervals ---900, 1,900, 2,900, 3,900, and 4,900 msec). Data collected were total number of hits and false alarms.

Choice reaction time. In this test subjects were instructed to place their finger tips on a central key and to strike one of four keys whenever one of four boxes displayed on the monitor lit up in red. The keys were set radially equidistant from the center key and corresponded spatially to the four boxes displayed on the screen. Forty trials were run. Mean reaction times were analyzed.

Descriptions of Performance Tests in Psychomotor Studies Continuous performance. This task used the same keyboard and apparatus as the choice reaction time task. The subject was required to touch the appropriate key whenever the corresponding box was illuminated. Each response triggered the immediate illumination of the next target, for a total of 180 trials. Mean reaction times were analyzed.

Finger tapping. In this test subject was required to tap a response key for 1 min. with the index finger of their dominant hand. The number of taps was recorded.

APPENDIX 1 (CONT.)

Descriptions of Performance Tests in Psychomotor Studies

Verbal free recall: Buschke selective reminding. The subject was presented with 20-word lists on the monitor at a rate of one word/3 sec. After each presentation the subject was given 90 sec. to recall as many words as possible. The subject was then reminded just of those items which were not recalled on the previous trial and required to recite as many items as possible from the entire list. A total of four trials was run. The measures analyzed were the mean number of words recalled over four trials and the "list-learned" score. This is the number of words recalled on the first trial and on all subsequent trials.

Delayed recall and recognition. Following a delay of 30 min., during which time other cognitive tests were administered, the subject was given 90 sec. to recall as many words as possible from the list of words used in the verbal recall task. This was followed by a forced choice recognition procedure in which the subject was presented with a list of three words (the target word and two semantically related words) and had to identify the previously seen word. The number of words correctly recalled and recognized was recorded.

Forwards and backwards digit span. This test consisted of two parts. The subject was first required to recall (by touching numbers in a grid) sequences of digits displayed on the computer screen, in the order in which they appeared. The number of digits in a sequence increased by one every time the subject made a correct response, up to a maximum of nine digits. If subjects made an error they were given another trial with the same number of digits. This was followed by backwards digit span in which the subject was required to recall digit sequences in reverse order. In both cases the test was terminated when the subject failed to correctly recall two sequences at a particular span length, or recalled nine digits correctly. The measure analyzed was the span length.

Critical flicker fusion thresholds. These were determined using the Leeds Critical Flicker Fusion tester. Four alternating binocular ascending and descending threshold determinations were run to give a single mean estimate of threshold.

Digit Symbol Substitution. This test consists of four printed rows of 125 blank squares, each headed with a digit from 1 to 9 in random sequence. An association key at the top of the page displays 9 consecutively numbered squares with a different letter-like symbol below each digit. Following a practice trial at the start of each session, 90 seconds will be allowed for rapidly writing the appropriate symbol under each numbered square as displayed in the association key. The number of squares correctly completed will be recorded as the score.

APPENDIX 1 (CONT.)

Descriptions of Performance Tests in Psychomotor Studies

Driving-Related Skills Tests In Studies 014 and 015

Divided-Attention Test (DAT)

Because of its high-demand characteristics, DAT serves as an analogue of the demands of driving. It requires concurrent performance of tracking and a visual search task. To perform the pursuit tracking task, which appears on a computer screen in the center of the visual field, subjects use a joystick to control a white, cross shape cursor. They pursue a red ball moving horizontally in response to a forcing function. The objective is to keep the cross and ball as closely aligned as possible. Absolute tracking error is recorded for this task

The second component of DAT is a visual search task which appears on two computer screens located to the left and right of central vision. Number arrays (two rows of three numbers) appear above and below center of both screens for a total of four displays located in peripheral vision. Subjects must monitor all four arrays and respond by pressing the corresponding button whenever the target number "2" appears. The numbers change continually and at random with the constraint. Response times and number of errors (misses, false alarms, incorrect responses) are recorded. The means for response times are calculated for all targets. The maximum allowable time for responding to a target is ten seconds, and that value for each missed target enters the calculation of the mean for 48 responses.

Subjects can adopt different performance strategies in response to the difficult demands of DAT. They may, for example, maintain performance on a single component of the test, thereby restricting deficits largely to the other component. If a subject uses this strategy and focuses on the central tasks, the visual search component of DAT will be impaired but tracking will show little treatment effect. For this reason, a measure of total test performance is calculated. Tracking error and visual search response time are converted to standardized scores which are combined to create a single measure of DAT performance.

APPENDIX 1 (CONT.)

Descriptions of Performance Tests in Psychomotor Studies

Critical Tracking Test (CTT)

The measure obtained from this high demand task reflects the ability to focus attention during short duration trials. Subjects use a rotary control to manipulate a vertical arrow with the objective being to keep the arrow at the center of the display as long as possible. The instability of the arrow's movement increases over time within a trial, leading to control loss and the end of the trial, typically in 60 seconds or less. The subject's score is the difficulty level (lambda) achieved immediately prior to loss of control with better performance producing both a higher lambda and longer test duration. The average duration of the 20-trial, self-paced test is 15 minutes.

Vigilance (VIG)

The low demand characteristics of VIG model the attention requirements of a monotonous task performed in an uneventful environment. An example of such a task in the context of driving would be prolonged nighttime driving on a straight roadway with low traffic density. Performance-degrading drowsiness may not be measurable with demanding tests which are themselves alerting. VIG is uniquely important in a test battery, because its display and the infrequent signals are non-arousing. Drowsiness is not offset by task demands, and effects of low levels of sedation can be measured.

The 40-minute VIG test is displayed as a circle of small squares on a computer screen. Subjects monitor a large square as it moves clockwise around the circle from one position to the next. A signal, to which subjects respond by keypress, is the skip of one position by the larger square. The 32 signals occur at random times and positions with the constraint that eight signals occur within each ten minutes of the test. Response times (with a 5 second maximum allowable response time) and number of errors (missed signals and false alarms) are recorded.

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

ATTACHMENTS

Attachments

1. Current Prescription Package Circular
2. Proposed OTC Label and Package Insert
3. Published Cyclobenzaprine Studies

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

ATTACHMENT 1:
CURRENT PRESCRIPTION
FLEXERIL PACKAGE CIRCULAR

MERCK & CO., INC.
West Point, PA 19486, USA

7897215

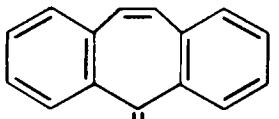
TABLETS

FLEXERIL®

(CYCLOBENZAPRINE HCl)

DESCRIPTION

Cyclobenzaprine hydrochloride is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N \cdot HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(5*H*-dibenzo[*a*,*d*] cycloheptен-5-ylidene)-*N*, *N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



$HCCH_2CH_2N(CH_3)_2 \cdot HCl$

FLEXERIL® (Cyclobenzaprine HCl) is supplied as 10 mg tablets for oral administration.

Tablets FLEXERIL contain the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Cyclobenzaprine HCl relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Cyclobenzaprine is well absorbed after oral administration, but there is a large intersubject variation in plasma levels. Cyclobenzaprine is eliminated quite slowly with a half-life as long as one to three days. It is highly bound to plasma proteins, is extensively metabolized primarily to glucuronide-like conjugates, and is excreted primarily via the kidneys.

No significant effect on plasma levels or bioavailability of FLEXERIL or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of FLEXERIL and aspirin is usually well tolerated and no unexpected or serious clinical or laboratory adverse effects have been observed. No studies have been performed to indicate whether FLEXERIL enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of FLEXERIL in acute musculoskeletal conditions.

Clinical Studies

Controlled clinical studies show that FLEXERIL significantly improves the signs and symptoms of skeletal muscle spasm as compared with placebo. The clinical responses include improvement in muscle spasm as determined by palpation, reduction in local pain and tenderness, increased range of motion, and less restriction in activities of daily living. When daily observations were made, clinical improvement was observed as early as the first day of therapy.

* Registered trademark of MERCK & CO., Inc.

Eight double-blind controlled clinical studies were performed in 642 patients comparing FLEXERIL, diazepam**, and placebo. Muscle spasm, local pain and tenderness, limitation of motion, and restriction in activities of daily living were evaluated. In three of these studies there was a significantly greater improvement with FLEXERIL than with diazepam, while in the other studies the improvement following both treatments was comparable.

Although the frequency and severity of adverse reactions observed in patients treated with FLEXERIL were comparable to those observed in patients treated with diazepam, dry mouth was observed more frequently in patients treated with FLEXERIL and dizziness more frequently in those treated with diazepam. The incidence of drowsiness, the most frequent adverse reaction, was similar with both drugs.

Analysis of the data from controlled studies shows that FLEXERIL produces clinical improvement whether or not sedation occurs.

Surveillance Program

A post-marketing surveillance program was carried out in 7607 patients with acute musculoskeletal disorders, and included 297 patients treated for 30 days or longer. The overall effectiveness of FLEXERIL was similar to that observed in the double-blind controlled studies; the overall incidence of adverse effects was less (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

FLEXERIL is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

FLEXERIL (Cyclobenzaprine HCl) should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

FLEXERIL has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

Hypersensitivity to the drug.

Concomitant use of monoamine oxidase inhibitors or within 14 days after their discontinuation.

Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

Hyperthyroidism.

WARNINGS

Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

FLEXERIL may interact with monoamine oxidase (MAO) inhibitors. Hyperpyretic crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs.

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, FLEXERIL should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

** VALIUM® (diazepam, Roche)

Information for Patients

FLEXERIL may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions

FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.[†]

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with FLEXERIL for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in rats, mice and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to FLEXERIL. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when FLEXERIL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of FLEXERIL in pediatric patients below 15 years of age have not been established.

ADVERSE REACTIONS

The following list of adverse reactions is based on the experience in 473 patients treated with FLEXERIL in controlled clinical studies, 7607 patients in the post-marketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with FLEXERIL were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies	*Surveillance Program*
drowsiness	39%	16%
dry mouth	27%	7%
dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

Incidence Less Than 1 in 100

The following adverse reactions have been reported at an incidence of less than 1 in 100:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice and cholestasis.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Musculoskeletal: Local weakness.

[†] ULTRAM® (tramadol HCl tablets, Ortho-McNeil Pharmaceutical)

Nervous System and Psychiatric: Ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.

Skin: Sweating.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown

Other reactions, reported rarely for FLEXERIL under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a Whole: Chest pain; edema.

Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.

Digestive: Paralytic ileus, tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Myalgia.

Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Photosensitization; alopecia.

Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when FLEXERIL is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Manifestations: High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia, in addition to anything listed under ADVERSE REACTIONS. Based on the known pharmacologic actions of the drug, overdosage may cause drowsiness, hypothermia, tachycardia and other cardiac rhythm abnormalities such as bundle branch block, ECG evidence of impaired conduction, and congestive heart failure. Other manifestations may be dilated pupils, convulsions, severe hypotension, stupor, and coma.

The acute oral LD_{50} of FLEXERIL is approximately 338 and 425 mg/kg in mice and rats, respectively.

Treatment: Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis, followed by gastric lavage. After gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function must be instituted if there is any evidence of dysrhythmia. Maintenance of an open airway, adequate fluid intake, and regulation of body temperature are necessary.

The intravenous administration of 1-3 mg of physostigmine salicylate is reported to reverse symptoms of poisoning by atropine and other drugs with anticholinergic activity. Physostigmine may be helpful in the treatment of cyclobenzaprine overdose. Because physostigmine is rapidly metabolized, the dosage of physostigmine should be repeated as required, particularly if life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dosage of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.

Standard medical measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. When signs of cardiac failure occur, the use of a short-acting digitalis preparation should be considered. Close monitoring of cardiac function for not less than five days is advisable.

Anticonvulsants may be given to control seizures.

Dialysis is probably of no value because of low plasma concentrations of the drug.

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

DOSAGE AND ADMINISTRATION

The usual dosage of FLEXERIL is 10 mg three times a day, with a range of 20 to 40 mg a day in divided doses. Dosage should not exceed 60 mg a day. Use of FLEXERIL for periods longer than two or three weeks is not recommended. (See INDICATIONS AND USAGE).

HOW SUPPLIED

No. 3358 — Tablets FLEXERIL, 10 mg, are butterscotch yellow, 5-sided D-shaped, film coated tablets, coded MSD 931 on one side and FLEXERIL on the other. They are supplied as follows:

NDC 0006-0931-68 in bottles of 100
(6505-01-062-8010, 10 mg 100's)
NDC 0006-0931-28 unit dose packages of 100
(6505-01-110-9926, 10 mg individually sealed 100's).

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

ATTACHMENT 2:
PROPOSED FLEXERIL OTC
LABEL AND PACKAGE INSERT

PROPOSED
LABELING
REDACTED
CONFIDENTIAL
COMMERCIAL
INFORMATION

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

ATTACHMENT 3:
PUBLICATIONS

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

POSTMARKETING SURVEILLANCE STUDY